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Tier 3 Toxicity Value White Paper

Regional Tier 3 Toxicity Value Workgroup

OSWER Human Health Regional Risk Assessors Forum

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Disclaimer: This U.S. Environmental Protection Agency (EPA) document discusses the process of identifying and selecting Tier 3 toxicity values. This document is not a rule or regulation and it may not apply to a particular situation based upon the circumstances. This document does not change or substitute for any law, regulation, or any other legally binding requirement and is not legally enforceable. As indicated by the use of non-mandatory language such as "guidance," "recommend," "may," "should," and "can," it identifies policies and provides recommendations and does not impose any legally binding requirements.

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Acronyms and Abbreviations

ADP	Action Development Process
AEGL	Acute Exposure Guideline Levels
ATSDR	Agency for Toxic Substances and Disease Registry
BMDL	Below minimal detection limit
Cal/EPA	California Environmental Protection Agency
CERCLA	Comprehensive Environmental Response, Compensation, and Recovery Act
DoD	U.S. Department of Defense
ECOS	Environment Council of the States
EPA	U.S. Environmental Protection Agency
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
HEAST	Health Effects Assessment Summary Tables
HHMSSL	Human Health Medium-Specific Screening Level
HQ	Headquarters
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
ITER	International Toxicity Estimates for Risk
IUR	Inhalation unit risk
LOAEL	Lowest observable adverse effect level
LOEL	Lowest observed effect level
MCL	Maximum contaminant level
mg/kg-day	Milligrams per kilogram per day

MOA	Mechanism of action
MOE	Margin of exposure
MRL	Minimal risk level
NCEA	National Center for Environmental Health
NJDEP	New Jersey Department of Environmental Protection
NOAEL	No observed adverse effect level
NTP	National Toxicology Program
NYSDOH	New York State Department of Health
OECD	Organization for Economic Co-operation and Development
OEHHA	Office of Environmental Health Hazard Assessment
OEM	Office of Emergency Management
OEPI	Office of Policy, Economics & Innovation
OH2R2AF	OSWER Human Health Regional Risk Assessors Forum
OMB	Office of Management and Budget
OPM	Office of Program Management
OPP	Office of Pesticide Programs
ORCR	Office of Resource Conservation and Recovery
ORD	Office of Research and Development
OSRTI	Office of Superfund Remediation & Technology Innovation
OSWER	Office of Solid Waste and Emergency Response
OUST	Office of Underground Storage Tanks
PARMS	Policy Analysis & Regulatory Management Staff
PBPK	Physiologically-based pharmacokinetic
PCE	Perchloroethylene
PFOA	Perfluorooctanic acid

PFOS	Perfluorooctane
PMCAO	Program Management, Communications, and Analysis Office
ppm	Parts per million
PPRTV	Provisional Peer Reviewed Toxicity Values
RAGS	Risk Assessment Guidance for Superfund
RBC	Risk-based concentration
RCRA	Resource Conservation and Recovery Act
RfC	Reference concentration
RfD	Reference dose
RIVM	National Institute of Public Health and the Environment of the Netherlands
RME	Reasonable maximum exposure
RP	Responsible party
RSL	Regional Screening Level
SAB	Science Advisory Board
SPB	Science Policy Branch
STSC	Superfund Health Risk Technical Support Center
TCE	Trichloroethylene
WHO	World Health Organization

Tier 3 Toxicity Value White Paper [1]

1 Introduction

1.1 Purpose

The purpose of this white paper is to articulate the issues pertaining to Tier 3 toxicity values and provide recommendations on processes that will improve the transparency and consistency of identifying, evaluating, selecting, and documenting Tier 3 toxicity values for use in the Superfund and Resource Conservation and Recovery Act (RCRA) programs. This white paper will be used to assist regional risk assessors in selecting Tier 3 toxicity values as well as provide the foundation for future regional and national efforts to improve guidance and policy on Tier 3 toxicity values.

1.1.1 Specific Objectives

The specific objectives of this white paper are to:

- Inform the reader of the differences and similarities between Tier 3 toxicity values,
- Discuss existing criteria and guidance that are relevant to selecting the most scientifically defensible Tier 3 toxicity value,
- Compare the available options for identifying, evaluating, selecting, and documenting Tier 3 toxicity values,
- Provide specific examples of how Tier 3 toxicity values have been identified and selected by the regions, and
- Recommend a process for selecting Tier 3 toxicity values.

1.1.2 Scope

This white paper is limited to Tier 3 toxicity values as defined in Office of Solid Waste and Emergency Response (OSWER) Directive 9285.7-53 (2003 Toxicity Value Hierarchy) and provides recommendations on processes for identifying, evaluating, selecting, documenting, and communicating Tier 3 toxicity values for use in site-specific human health risk assessments.[2] This white paper has been reviewed by the regional risk assessors, and the recommendations are based on the consensus of the regional risk assessors. While not guidance or policy itself, the white paper is also written with the intent to assist

[1] *Disclaimer: This U.S. Environmental Protection Agency (EPA) document discusses the process of identifying and selecting Tier 3 toxicity values. This document is not a rule or regulation and it may not apply to a particular situation based upon the circumstances. This document does not change or substitute for any law, regulation, or any other legally binding requirement and is not legally enforceable. As indicated by the use of non-mandatory language such as "guidance," "recommend," "may," "should," and "can," it identifies policies and provides recommendations and does not impose any legally binding requirements.*

[2] The derivation of new toxicity values falls outside of the scope of this white paper.

others (regional risk assessors, regional risk assessment workgroups, Regional Toxics Integration Coordinators, and headquarters risk assessors) in developing formal or informal EPA regional and national guidance or policy.

1.2 Background

Toxicity values (including reference doses [RfD], reference concentrations [RfC], cancer slope factors, and inhalation unit risks) needed for use in human health risk assessment are generally derived by reviewing available dose-response data in animals or humans, selecting a point of departure in the data that is judged most suitable, and adjusting for associated uncertainties. Often, multiple data sets are available, and there may be a variety of options for deriving the toxicity values. In addition, there are a variety of options for fitting the data and selecting and applying uncertainty factors. For these reasons, there can sometimes be a number of alternative toxicity factors available from different sources for a specified chemical.

OSWER has developed a number of guidance documents which include recommendations for selecting toxicity values. The early guidance established the IRIS database as the preferred source for selecting toxicity values (EPA 1989, 1991, 1993). Subsequent guidance confirmed the preference for the use of IRIS values and made suggestions for appropriate sources of toxicological information that could be used for selecting or deriving toxicity factors in cases where no published IRIS value was available for a given chemical. These developments have led to the concept of applying a more formal or prescribed "hierarchy" for consulting data sources to select or derive toxicity values (EPA 2003, 2005, 2009). This section describes the existing policies used by the Superfund Program for selecting toxicity values, and when necessary, deriving appropriate values for site-specific risk assessment activities.

1.2.1 OSWER's Toxicity Value Hierarchy

1.2.1.1 Risk Assessment Guidance for Superfund (RAGS) Parts A and B

The first guidance on the hierarchy for selecting toxicity factors was provided in Risk Assessment Guidance for Superfund (RAGS) Part A (1989) and Part B (1991). These documents specify that the first preference is for toxicity values that are presented in EPA's Integrated Risk Information System (IRIS). The 1993 OSWER Directive titled "Use of IRIS Values in Superfund Risk Assessment" reconfirmed that IRIS values should be given the highest priority for application in Superfund risk assessments and that alternative toxicological information should only be considered on a case-by-case basis (http://www.epa.gov/oswer/riskassessment/pdf/irismemo.pdf). To this day, IRIS generally supersedes all other sources of toxicity information and is considered the "gold-standard" in terms of toxicological assessments. If no value was available in IRIS, the second preference was identified as the Health Effects Assessment Summary Tables (HEAST). HEAST provided up-to-date toxicity values in a tabular format, first quarterly and then annually for several years through 1997. Unlike IRIS, not all HEAST values went through a formal peer or EPA review process, and interim values were also included in the tables.

If toxicity values were not available on IRIS or in HEAST, then RAGS recommended, in no specified order, other sources such as EPA criteria documents (health advisory summaries), Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profiles, or provisional toxicity assessments prepared by the National Center for Environmental Assessment (formerly the Environmental Criteria and Assessment Office).

1.2.1.2 2003 Directive Human Health Toxicity Values in Superfund Risk Assessments

In 2003, OSWER Directive 9285.7-53 revised Superfund's hierarchy of human health toxicity values, providing three tiers of toxicity values.[3] There were two important reasons for updating the RAGS toxicity hierarchy. First, additional sources of peer-reviewed values had become available, such as EPA's Provisional Peer Reviewed Toxicity Values (PPRTVs). Second, HEAST, which had been identified in RAGS as the second choice for toxicity information, had not been updated since 1997.

The revised hierarchy provided three tiers of toxicity values: IRIS as the first tier, PPRTVs as the second tier, and "other toxicity values" as the third tier. Example sources of Tier 3 toxicity values included California EPA (Cal/EPA) toxicity values, ATSDR Minimum Risk Levels (MRLs), and HEAST.

1.2.1.3 RAGS Part E and F

RAGS Part E (Dermal Guidance) and RAGS Part F (Inhalation Guidance) were the first supplemental guidance documents to be published after the 2003 OSWER directive. Although RAGS Part E, which was released in 2004, does not reference the 2003 OSWER directive or previous toxicity value hierarchies, this guidance discusses a process for estimating dermal toxicity values by extrapolating from approved oral toxicity values. In 2009, RAGS Part F cited the 2003 OSWER directive as the appropriate hierarchy for selecting toxicity values. RAGS Part F notes that extrapolation of toxicity values from the oral to the inhalation exposure route may not be appropriate in all cases.

1.2.2 Limitations of OSWER Guidance on Tier 3 Toxicity Value Selection

When no Tier 1 or Tier 2 toxicity value is available, but there are several Tier 3 values, it is necessary to decide which Tier 3 value is most appropriate. The merit of these values may vary depending on the scientific quality and rigor of the underlying toxicological studies and analysis and the extent of the peer review. Development of some available values (such as ATSDR MRLs[4] and Cal/EPA toxicity values), includes extensive literature review, rigorous data analysis using up-to-date guidance and methods to derive a toxicity value, and thorough peer review. Development of other toxicity values is not

[3] As an OSWER Directive, the hierarchy is also used by the Office of Brownfields & Land Revitalization (Brownfields), the Office of Emergency Management (OEM), the Office of Resource Conservation and Recovery (ORCR), and the Office of Underground Storage Tanks (OUST).

[4] ATSDR MRLs are limited to non-cancer effects only, but can include chronic, subchronic, and acute values.

necessarily based strictly on risk assessment practices, but may consider other factors. EPA Office of Water maximum contaminant levels (MCLs), for example, may be based on technological limitations in measurement or implementation.

The 2003 OSWER directive provides only limited guidance on selection of Tier 3 toxicity values, recommending that priority should be given to studies that are the most current, transparent in terms of their study or derivation methods, and that have been peer reviewed. Given the wide variety of sources for Tier 3 toxicity values, further guidance is warranted to assist risk assessors to select the most appropriate available Tier 3 value for use at Superfund and RCRA sites.

1.2.3 November 2009 Regional Risk Assessors Meeting

During a session of the November 2009 EPA Region Risk Assessors meeting, the regional risk assessors presented and discussed the approaches, challenges, and limitations for identifying and selecting Tier 3 toxicity values. Specific issues covered during the session included, but were not limited to, existing processes that regional risk assessors were using for identifying and selecting Tier 3 toxicity values, differences between Tier 3 toxicity value sources (for example, derivation methods, transparency, and use of uncertainty factors), and who is responsible for and what could be done to improve the Tier 3 toxicity value selection process. As a result of the presentations and ensuing discussions, the Regional Tier 3 Toxicity Value Workgroup was formed, consisting of a small group of regional risk assessors. The workgroup was given the broad task of developing processes for improving the selection of Tier 3 toxicity values. After the November meeting, the members of the workgroup met and charged themselves with building upon OSWER's toxicity value hierarchy by developing, evaluating, and recommending a processes for identifying and selecting Tier 3 toxicity values. Given that the charge and tasks were broad in scope, additional members and contacts were added to the workgroup, including representatives from headquarters and the regions responsible for the Regional Screening Level Table. Also, consistent with the workgroup's charge and tasks specified during the November 2009 meeting, the workgroup decided that these efforts would be documented in the form of a white paper.

2 Tier 3 Toxicity Values

Currently, there are a myriad of potential sources of ready-made Tier 3 toxicity values and additional sources that provide the data necessary to derive a Tier 3 toxicity value. The purpose of this section is to provide examples from each of these sources, since there are far too many to list. This section will also introduce the similarities and differences between the sources of potential ready-made Tier 3 toxicity values.

2.1 Sources

Tier 3 toxicity values and toxicity data can be derived from state, federal (U.S.), and international sources. The following sections provide examples of some of the most commonly used state, federal and international sources of Tier 3 toxicity values and toxicity data used by risk assessors.

2.1.1 Federal (Internal and External to EPA)

Both EPA and its individual program offices can be useful sources of Tier 3 toxicity values and data. Before a chemical file is posted on the IRIS database in its final form, it must undergo a series of drafts, internal and external peer reviews, and revisions. A major part of this process is development of the draft toxicological review document for the individual chemical. This document details all of the available human and animal toxicity data evaluated and the recommendation for a quantitative cancer or noncancer toxicity value. Although the use of draft IRIS toxicity values as Tier 3 values is generally not appropriate except as indicated in USEPA, 2003, the toxicity values and supporting data in the draft IRIS toxicological reviews can be useful when evaluating a potential Tier 3 toxicity value from another source. These draft documents are useful because the literature searches have been completed and documented, the toxicity values derived using EPA-recommended methodologies, and to a greater or lesser extent have undergone peer review. These draft toxicological reviews can be obtained from the Region's IRIS consensus reviewer and are posted on the web during the public review and comment period.

Individual program offices often develop sources of toxicity values, which are not researched and peer reviewed to the same extent as IRIS files, but are useful for specific chemicals and routes of exposure. One example is the HEAST (http://epa-heast.ornl.gov/) developed for EPA's Superfund and RCRA hazardous waste programs. The Office of Pollution Prevention and Toxics Substances maintains the Acute Exposure Guidelines Levels (AEGLs) database, which provides acceptable concentrations for once in a lifetime, short-term exposures to airborne concentrations of acutely toxic, high priority chemicals (http://www.epa.gov/oppt/aegl/index.htm). These acute values are based on the recommendations of a federal advisory committee consisting of scientists from the public and private sectors. The Office of Pesticide Programs and the National Center for Environmental Assessment in the Office of Research and Development (ORD) are other potential sources of toxicity values.

Outside of EPA, perhaps the best known source of federal toxicity values is ATSDR. This agency develops toxicological profiles for individual chemicals (available at http://www.atsdr.cdc.gov/toxprofiles/index.asp), which are similar to the IRIS Toxicological Reviews. In addition to a review of the available human and animal toxicity studies, the profiles recommend quantitative values for risk management decision-making.

2.1.2 State Toxicity Values

A number of state environmental regulatory programs develop and maintain databases of quantitative toxicity values. Perhaps the best known of these is the Cal/EPA toxicity values available on its Internet website at http://www.oehha.ca.gov/risk/chemicalDB/index.asp. Examples of other state databases of toxicity values include New Jersey Department of Environmental Protection (http://www.state.nj.us/dep/dsr), and the Texas Department of Environmental Quality (http://www.tceq.texas.gov/toxicology). States have also derived toxicity values for specific chemicals and routes of exposure. For example, the New York State Department of Health (NYSDOH) developed an air criteria document for trichloroethylene in 2006, which evaluated and derived noncancer and cancer toxicity values (NYSDOH 2006).

2.1.3 International Community

Quantitative toxicity information can be found on the websites for many international regulatory agencies. For example, Health Canada prepares screening assessments of priority chemicals under the Canadian Environmental Protection Act of 1999 (http://www.chemicalsubstanceschimiques.gc.ca/plan/index-eng.php). One database that provides information from a number of international sources is the International Toxicity Estimates for Risk (ITER) database, which can be found at http://iter.ctcnet.net/publicurl/pub_search_list.cfm. In addition to EPA's IRIS and the ATSDR databases, this site includes toxicity values from Health Canada, the International Agency for Research on Cancer (IARC), the International Programme on Chemical Safety (IPCS), the National Institute of Public Health and the Environment of the Netherlands (RIVM), as well as peer-reviewed values by independent parties, such as Toxicological Excellence for Risk Assessment.

2.1.4 Databases for Developing Toxicity Values

In addition to state, federal, and international databases with cancer and noncancer toxicity values, there are also a tremendous number of resources that can be researched to develop toxicity values for specific chemicals.[5] EPA has recently released ToxRefDB (http://actor.epa.gov/toxrefdb/faces/Home.jsp). This database captures detailed study design, dosing, and observed treatment-related effects on thousands of *in vivo* animal toxicity studies on hundreds of chemicals. This database was developed by the National Center for Computational Toxicology in

[5] The derivation of new toxicity values falls outside of the scope of this white paper. However, state, federal, and international databases can be useful resources for evaluating existing Tier 3 toxicity values.

partnership with the Office of Pesticide Programs. Examples of other databases include the National Library of Medicine Toxnet (http://toxnet.nlm.nih.gov/) and Micromedex (http://www.micromedex.com/products/hcs/), and the National Toxicology Program (NTP; http://ntp.niehs.nih.gov/). NTP provides toxicological information on over 500 chemicals through the publication of general Technical Reports on chemicals and chemical mixtures and the Scientific Review documents for chemicals and chemical agents which are listed in the Report on Carcinogens documents.

2.2 Similarities and Differences In How Toxicity Values Are Derived

As shown above, there are a large number of state, federal, and international resources for either obtaining or developing Tier 3 toxicity values. When obtaining toxicity values and data from these sources it is important to recognize that there are similarities and differences in how they develop toxicity values. This is important when comparing methodologies from external agencies and organizations to EPA's methodologies, as well as when comparing competing toxicity values. Similarities and differences may arise from the following elements:

- The quality and usability of the animal and human studies used to derive the toxicity values
- How adverse and critical effects are defined, and
- The methodologies used to derive the cancer or noncancer toxicity value

The first two elements are common to most of the databases and toxicity values discussed above. The methodologies used to calculate quantitative values are typically specific to the regulatory agency involved. These elements or guiding principles, which will be further discussed in Section 5.3.2, will serve as the basis for critical reviews of potential Tier 3 toxicity values.

In the case of competing toxicity values, differences between values may also be simply a result of the age of the toxicity values. Newer values will likely have more studies underlying their derivation. In addition, newer values may incorporate more current methods for evaluating dose/response relationships, such as physiologically-based pharmacokinetic (PBPK) modeling.

Although not discussed further in this white paper, a basic understanding of how to evaluate and assess the data usability of toxicity studies, identify the adverse and critical effect levels in a study, and evaluate the regulatory-specific methodologies used to derive cancer and noncancer toxicity values is useful for comparing, selecting, and developing chemical-specific toxicity values from multiple databases (Ibid).

3 Existing Publications Relevant to Tier 3 Toxicity Value Evaluation, Selection, and Use

This section summarizes existing publications that are relevant to the evaluation, selection and use of Tier 3 toxicity values. These publications include documents internal and external to EPA and include policy directives, guidance documents, handbooks, guidelines, and issue papers. In addition to summarizing these documents, the purpose of this section is to draw attention to elements of these documents that are critical in the evaluation of potential Tier 3 toxicity values.

3.1 Internal EPA Documents

3.1.1 2003 Hierarchy (OSWER Directive 9285.7-53)

As discussed in Section 1.1.1.2, EPA's Superfund program revised its hierarchy of human health toxicity values to incorporate EPA's PPRTVs and address the aging HEAST toxicity values. Although the 2003 guidance established an overall hierarchy for selecting toxicity values, it did not attempt to rank Tier 3 sources. Instead, it provides examples of Tier 3 sources and general recommendations regarding the prioritization of Tier 3 toxicity values. Specifically, in reference to Tier 3 toxicity values, the directive states:

> *Priority should be given to sources that provide toxicity information based on similar methods and procedures as those used for Tier I and Tier II, contain values which are peer reviewed, are available to the public, and are transparent about the methods and processes used to develop the values. Consultation with the Superfund Health Risk Technical Support Center (STSC) or headquarters program office is recommended regarding the use of the Tier 3 values for Superfund response decisions when the contaminant appears to be a risk driver for the site. In general, draft toxicity assessments are not appropriate for use until they have been through peer review, the peer review comments have been addressed in a revised draft, and the revised draft is publicly available.*

Although the directive does not go into great detail on selection of Tier 3 toxicity values, it is clear that it recommends that risk assessors select values that are derived using toxicological and risk assessment methods that are:

(1) Consistent with the Agency's methodologies;
(2) Transparent;
(3) Publicly available; and
(4) Have undergone peer review.

In addition, the directive recommends the involvement of ORD (Superfund Technical Support Center [STSC]) and headquarters and cautions against the use of draft toxicity values to ensure the scientific defensibility of Tier 3 toxicity values, especially risk-driving chemicals.

3.1.2 Peer Review Handbook

As indicated in the 2003 hierarchy memorandum and other publications specific to toxicity value selection and use (see for example, EPA 2009; ECOS 2007), peer review is one of several critical elements in selecting or giving preference to one toxicity value over another. Although not necessarily specific to toxicity value selection, EPA's Peer Review Handbook (EPA 2006) provides important information that is applicable to the evaluation and selection of Tier 3 toxicity values. The 3rd edition of the peer review handbook defines peer review as the following:

> *Peer review is a documented critical review of a specific Agency scientific and/or technical work product. Peer review is conducted by qualified individuals (or organizations) who are independent of those who performed the work, and who are collectively equivalent in technical expertise (i.e., peers) to those who performed the original work. Peer review is conducted to ensure that activities are technically supportable, competently performed, properly documented, and consistent with established quality criteria. Peer review is an in-depth assessment of the assumptions, calculations, extrapolations, alternate interpretations, methodology, acceptance criteria, and conclusions pertaining to the specific major scientific and/or technical work product and of the documentation that supports them. Peer review may provide an evaluation of a subject where quantitative methods of analysis or measures of success are unavailable or undefined such as research and development. Peer review is usually characterized by a one-time interaction or a limited number of interactions by independent peer reviewers. Peer review is encouraged during the early stages of the project or methods selection, and/or as part of the culmination of the work product, as appropriate. Regardless of the timing of peer review, the goal is ensuring that the final product is technically sound. (USEPA, 2006a)*

The importance of peer-review is re-affirmed in EPA's 2006 peer review policy, which states:

> *Peer review of all scientific and technical information that is intended to inform or support Agency decisions is encouraged and expected. Influential scientific information, including highly influential scientific assessments, should be peer reviewed in accordance with the Agency's Peer Review Handbook. All Agency managers are accountable for ensuring that Agency policy and guidance are appropriately applied in determining if their work products are influential or highly influential, and for deciding the nature, scope, and timing of their peer review. For highly influential scientific assessments, external peer review is the expected procedure. For influential scientific information intended to support important decisions, or for work products that have special*

importance in their own right, external peer review is the approach of choice (USEPA, 2006b).[6]

3.1.3 RAGS Part F

RAGS Part F also provides guidance on evaluation and selection of a Tier 3 toxicity value. In reference to EPA's toxicity value hierarchy, RAGS Part F states, "Priority in Tier 3 should be given to sources that are the most current and those that are peer reviewed. Consultation with the Superfund Headquarters office is recommended regarding the use of Tier 3 values for Superfund response decisions when the contaminant appears to be a risk driver for the site." In addition, this guidance provides a list of circumstances when route-to-route extrapolations from oral toxicity values might not be appropriate. This information could be useful in evaluating Tier 3 toxicity values that are based on route-to-route extrapolations.

3.1.4 Risk Assessment Guidelines

Multiple risk assessment guidelines have been published by EPA ranging from the Guidelines for Mutagenicity Assessment (1986) to the 2005 Guidelines for Carcinogen Risk Assessment. These guidelines , as well as other guidance documents pertaining to development of toxicity values (1994 *Methods for Derivation of Inhalation Reference Concentrations [RfCs] and Application of Inhalation Dosimetry*) provide specific guidance (including criteria to be met) on how the Agency derives toxicity values. These documents have and will continue to serve as the benchmark for evaluating toxicity values external to EPA.

3.1.5 Harmonized Test Guidelines

EPA's harmonized test guidelines (http://www.epa.gov/ocspp/pubs/frs/home/guidelin.htm) are documents that specify methods for use in testing pesticides and toxic substances and developing test data for submittal to the Agency. The guidelines typically specify the species to be tested, routes of administration, doses to be administered, and duration of study and endpoints to be assessed. These guidelines serve as the "gold standard" for performing toxicity testing and studies and, similar to the risk assessment guidelines discussed in Section 3.1.4, serve as a benchmark for evaluating the adequacy of a toxicity value's underlying study or studies.

3.2 Environmental Council of the States

[6] Influential scientific and highly influential scientific assessments involve precedential, novel, "cutting edge," or controversial issues, or the Agency has a legal or statutory obligation to conduct a peer review. Highly influential scientific assessments have a higher degree of influence, substance, interagency interest, and economic impact (EPA 2006a).

In April 2007, the Environmental Council of the States-U.S. Department of Defense Sustainability Work Group (ECOS-DoD Sustainability Work Group) released the issue paper (ECOS paper) titled "Identification and Selection of Toxicity Values/Criteria for Comprehensive Environmental Response, Compensation, and Recovery Act (CERCLA) and Hazardous Waste Site Risk Assessments in the Absence of IRIS Values." The ECOS paper, which was written in collaboration with EPA, Cal/EPA, and Department of Defense (DoD) scientists and risk assessors, is intended to provide guidance and a suggested framework for identifying and selecting toxicity values in the absence of IRIS values. The ECOS paper provides this guidance and framework in the form of seven preferences for identifying and ranking toxicity values. These preferences are provided below.

(1) *There should be a preference for transparent assessments (in which toxicity values are derived), that clearly identify the information used and how it was used.*

(2) *There should be a preference for assessments which have been externally and independently peer reviewed, where reviewers and affiliations are identified. Other things being equal, there should also be a preference for assessments with more extensive peer review. Panel peer reviews are considered preferable to letter peer reviews.*

(3) *There should be a preference for assessments that were completed with a previously established and publicly available methodology. Methodologies that themselves were externally peer reviewed are preferred over those that were not externally peer reviewed.*

(4) *While there should be a preference for assessments using established methodologies to derive toxicity values, these methodologies should also be informed by the current best scientific information and practices. New assessment methodologies should provide reproducible results and meet quality assurance and quality control requirements.*

(5) *There should be a preference for assessments that consider the quality of studies used, including the statistical power or lack thereof to detect effects; that corroborate data amongst pertinent studies; and that make best use of all available science.*

(6) *There should be a preference for assessments and values which are publicly available or accessible. There may be a further preference for toxicity assessments that invited and considered public comment (as well as, but not in lieu of, external peer review).*

(7) *Other things being equal, there should be a preference for toxicity values that are consistent with the duration of human exposure being assessed. For example, an externally peer reviewed subchronic reference dose (RfD) should be preferred to an externally peer reviewed chronic RfD when assessing an exposure of 2 years for non-cancer toxicity.* (ECOS 2007)

In conjunction with these seven preferences, the ECOS paper provides additional recommendations relevant to the selection of toxicity values. They include the overarching principle that risk assessors should continue to identify the most scientifically defensible toxicity value and that the selecting individuals have an understanding of the available sources of toxicity data and their strengths and weaknesses so that the most appropriate toxicity value is selected. Furthermore, although the seven preferences are generally intended for existing toxicity values, the ECOS paper specifically states that the preferences may be "used if an agency or party would like to propose an alternative to a toxicity value" (ECOS 2007).

4 Current and Past Regional Practices in Identifying and Selecting Tier 3 Toxicity Values

The purpose of this section is to summarize past and current practices used by regional and headquarters risks assessors to evaluate and select Tier 3 toxicity values. Specifically, this section discusses the evaluation and selection processes employed by the regional risk assessors to derive the regional screening levels. Also, this section provides detailed summaries of Tier 3 toxicity value consultations provided by regional and headquarters risk assessors.

4.1 Regional Screening Levels Table (Selection Process)

Risk-based screening levels for soil, air, and water have been in existence for nearly 20 years in EPA's Superfund Program. Similar to human health risk assessments, screening levels are derived using chemical-specific toxicity values combined with standard exposure factors that reflect Superfund's concept of a reasonable maximum exposure (RME). They have traditionally represented the point of departure of an excess lifetime cancer risk level of 1E-06 or a Hazard Quotient of 1 for noncancer effects.

In the past, risk-based screening levels were compiled in individual regional tables such as the Risk-Based Concentrations (RBC) table published by Region 3, the Human Health Medium-Specific Screening Levels (HHMSSL) table published by Region 6, and the Preliminary Remediation Goals (PRG) table published by Region 9. In general, if a substance had been assigned an EPA toxicity value, it was listed in the individual regional screening tables. In the case where a substance had more than one possible toxicity value, a toxicity hierarchy first described in RAGS Part A was applied. In some cases, each Region developed its own unique values (e.g., Region 3 RBCs for Fish Consumption).

One consequence of the 2003 toxicity values hierarchy memorandum (Human Health Toxicity Values in Superfund Risk Assessments, OSWER Directive 9285.7-53, December 5, 2003) was that the risk screening tables needed to be revised to reflect the new Agency preference for toxicity values. The guidance was clear with respect to the first two tiers in the hierarchy, and these tiers were used as "defaults" in the regional tables. However, it was less clear what was to be used as a Tier 3 source when there are competing sources. This lack of clarity could have led to inconsistencies in the regional screening tables if, for example, Region 3 used a different Tier 3 source than Region 9 or Region 6.

The regional offices that created screening tables have had a long history of communication and coordination to reduce (if not avoid) inconsistencies among the individual tables. Nonetheless, inconsistencies still existed. An important milestone was reached in 2008, when the various regional tables were harmonized into a single majority-consensus table known as the Regional Screening Levels (RSL) table. This table updated and superseded previous regional tables. Individual Regions are still able to develop independent (or non-consensus) screening values, however, they are not published as part of the RSL table. Individual Regions may also choose Tier 3 values different from the RSL table. It is not the responsibility of the RSL table workgroup to choose for, or dictate to the Regions. The RSL table workgroup merely makes recommendations. Representatives from all EPA regions and HQ are

encouraged to participate in the RSL table workgroup so that their valuable input is incorporated in the periodic updates and revisions to the screening table.

Establishing which toxicity values to use when there are no applicable Tier 1 or Tier 2 values is a challenge because the 2003 guidance did not provide a ranking or hierarchy for Tier 3 sources The RSL workgroup has proposed and implemented a tentative ranking of Tier 3 sources to include in the screening table. The RSL workgroup readily acknowledges that other toxicity values (e.g., State values) could be used to develop the screening values. It is NOT the mission or goal of the RSL workgroup to independently develop Tier 3 toxicity reference values in the absence of other sources, nor is it a practice of the workgroup to review values from all potential sources.

At present, the Tier 3 toxicity values from the following sources in the order in which they are presented below are used as the defaults in the RSL tables.

(1) The ATSDR Minimal Risk Levels (MRLs)
(2) Cal/EPA, Office of Environmental Health Hazard Assessment (OEHHA), toxicity values
(3) PPRTV Appendix "Screening Toxicity Values"
(4) HEAST

These sources are credible (rely on best available science, have undergone a high degree of scrutiny and peer review, are often considered by other Agencies).

An RSL calculator is also provided, which allows the user to use a different toxicity value or exposure assumptions other than the defaults. The RSL group anticipates that RSL's provisional hierarchy may change in the future to reflect recommendations in this white paper.

4.2 Tier 3 Toxicity Value Consultations

When there is no established Tier 3 value for high-priority chemicals that are likely to be risk drivers at a site, the regions have often performed their own evaluations of the science and/or sought headquarters guidance. With respect to headquarters consultations, key offices that have been involved include, but are not necessarily limited to, OSWER/OSRTI/SPB, OSWER/OEM, OSWER/OPM/PARMS, OSWER/ORCR/PMCAO, and ORD/NCEA. Below are several examples of how Tier 3 values have been evaluated and selected in the past at the regional and headquarters level.

4.2.1 Chromium (VI)

The 1998 IRIS file for chromium (VI) identified it as an inhalation carcinogen and provided an inhalation unit risk (IUR), but oral carcinogenicity could not be determined because no data were located in the available literature that suggested it was carcinogenic by the oral route of exposure (EPA 1998). However, several years later, a study by the National Toxicology Program (NTP) stated that oral exposure to chromium (VI) "provided *clear evidence of carcinogenic activity* in male and female rats and

mice based on the presence of benign and malignant tumors in rat oral mucosa and mouse small intestine" (NTP 2008) and suggested that the compound may be carcinogenic by mutagenic mode of action. In response to this study, some states (New Jersey and California) began the process of revising their water and soil standards based on the NTP study. EPA's Office of Pesticide Programs (OPP) also developed an oral slope factor and published a journal article on the chemical's mutagenic mode of action to support its risk assessment of chromated copper arsenate (McCarroll et al. 2010). In November 2008, the IRIS program began the reassessment of chromium VI for the oral route of exposure.

Region 2 appealed to headquarters in 2009 for guidance while working on a removal site because the state of the science had evolved faster than IRIS could be updated and several potential Tier 3 toxicity values were available. Specifically, Region 2 requested consultation on the use of New Jersey's oral slope factor (NJDEP 2009). In this request, Region 2 noted that although several potential Tier 3 sources are available, only New Jersey's oral slope factor met all the criteria in the 2003 hierarchy directive. The request was submitted to the Senior Science Advisor for OSWER on August 17, 2009, who consulted with representatives of OSRTI and OEM and concurred with this conclusion in an e-mail on September 28, 2009 (see Appendix B).

4.2.2 Perfluorooctanic Acid and Perfluorooctane Sulfonate

Perfluorooctanic acid (PFOA) and perfluorooctane sulfonate (PFOS) are emerging contaminants that have been found at sites in Region 4 and other regions. Because no toxicity values for these compounds are currently available in the IRIS or PPRTV databases, Region 4 requested that OSWER recommend what toxicity values would be appropriate to use. In response, OSRTI and OEM consulted scientists from EPA's Office of Water, Office of Pollution and Toxic Substances, and the Office of Research and Development regarding the use of the Office of Water's 2009 Provisional Health Advisories for PFOA and PFOS.

In an October 28, 2009, memorandum (see Appendix B), OSRTI and OEM recommended use of the provisional drinking water advisories for PFOA and PFOS and interim subchronic RfDs based on the advisory levels. Because the drinking water advisories address only water, OSWER's consultation included derivation of subchronic RfDs so that they could be used to derive removal action levels or screening levels for water and other media. The memorandum also outlines the ways the Provisional Health Advisories meet the criteria for a Tier 3 toxicity value as established in the hierarchy directive. Specifically, the consultation memorandum notes that the provisional advisories underwent internal and external review and draws attention to similarities between the Office of Water's methodology for deriving provisional advisory levels (and the subsequent subchronic RfDs) and IRIS assessments (deriving toxicity values using Benchmark Dose Level (BMDL), no observed adverse effects level [NOAEL], or lowest observed adverse effects level [LOAEL]).

4.2.3 Perchloroethylene

At about the time the 2003 toxicity value hierarchy was being finalized and released to the regional risk assessors, regions sent inquiries to OSWER regarding the use of Cal/EPA's cancer toxicity values for perchloroethyelene (PCE). Found at nearly half of all Superfund sites (ATSDR 1997), including numerous vapor intrusion sites, having toxicity values for this chemical was key to moving risk assessments and remedy decisions forward. Moving these activities forward was of special concern given that health organizations, such as IARC, had classified PCE as a probable human carcinogen (IARC 1995).[7]

In response, the Deputy Director of the Office of Emergency and Remedial Response (currently OSRTI), in consultation with the STSC, sent a letter to Region 10 on June 12, 2003, supporting the use of Cal/EPA's IUR and oral slope factor (see Appendix B), noting that there are similarities between how Cal/EPA and the IRIS program develop toxicity values and that Cal/EPA's presentation on how the toxicity values were developed is full, complete, and transparent. In regards to transparency and the use of the values in Superfund Program decision-making, the letter recommended that the appropriate documentation or link to the Cal/EPA website be provided. In addition, the letter included an excerpt from a Cal/EPA technical support document pertaining to PCE's inhalation unit risk value.

4.2.4 Trichloroethylene

Trichloroethylene (TCE), which is found at more than 1,500 sites, has a long and complicated history at EPA, especially within the IRIS and Superfund Programs. The IRIS cancer assessment and cancer toxicity values for TCE, which were released in 1987, were withdrawn in 1989.[8] Between 1989 and 2001, regions generally relied on the withdrawn values. In 2001, NCEA completed a preliminary draft assessment of the health risks posed by TCE. The new toxicity values, especially the cancer toxicity values, dramatically increased the calculated risks at the same exposure. Although these values were not loaded into the IRIS database, some regions continued to use them since they were briefly endorsed by STSC. After review by EPA's Science Advisory Board (SAB) in 2002, STSC no longer supported the use of the 2001 draft values. However, several regions continued to use the 2001 draft toxicity values. After the 2003 toxicity hierarchy memorandum was released, some regions began using the Cal/EPA toxicity values for TCE or a combination of Cal/EPA toxicity values and the 2001 draft toxicity values, while others continued to use only the 2001 draft toxicity values. The Region 9 PRG, Region 3 RBC, and Region 6 MSSLs used the 2001 draft noncancer and cancer toxicity values up until approximately the time the tables were consolidated into the RSLs in 2008. In 2008, the RSL tables began using the Cal/EPA cancer toxicity values.

[7] Prior to PCE's final Toxicological Review, which was posted on IRIS on February 10, 2012, IRIS only provided an RfD.

[8] TCE's final Toxicological Review was posted on IRIS on September 28, 2011.

In 2006, the NYSDOH released the *Trichloroethene Air Criteria Document*. That document, which underwent peer review, provided a noncancer inhalation toxicity value comparable to an EPA RfC. Because the NYSDOH toxicity value was final, had undergone peer-review, and its derivation was transparent, some regions began considering use of the value to assess noncancer health risks. Its use in risk assessments was significant, especially with respect to the vapor intrusion into indoor air pathway, because the NYSDOH value results in residential indoor air noncancer screening levels corresponding to a cancer risk of approximately 1E-05. In comparison, Cal/EPA provides a noncancer chronic REL that is 60 times greater than the NYSDOH value.

In 2008, Region 10 advised its states about Region 10's evaluation of TCE and provided two options for evaluating cancer risk: (1) use the geometric midpoint of the slope factor range from the 2001 NCEA assessment, or (2) use the Cal/EPA oral slope factor and inhalation unit risk, but adjust them upward by a factor of 10. When noncancer health hazards are evaluated, Region 10 recommended using the NYSDOH criterion.

In January 2009, OSWER released guidance on the recommended cancer and noncancer toxicity values (Cal/EPA cancer toxicity values and the NYSDOH noncancer inhalation toxicity value) (see Appendix B). The memorandum provided an extensive summary and evaluation of the available toxicity values from Cal/EPA, NYSDOH, and the Indiana Department of Environmental Management. It included a discussion on the toxicity values' underlying studies and methods used to derive the toxicity values and a detailed comparison of the competing noncancer inhalation toxicity values. However, the memo was withdrawn by OSWER in April 2009 to further evaluate the recommendations regarding the noncancer toxicity values for use in inhalation risk assessments (see Appendix B).

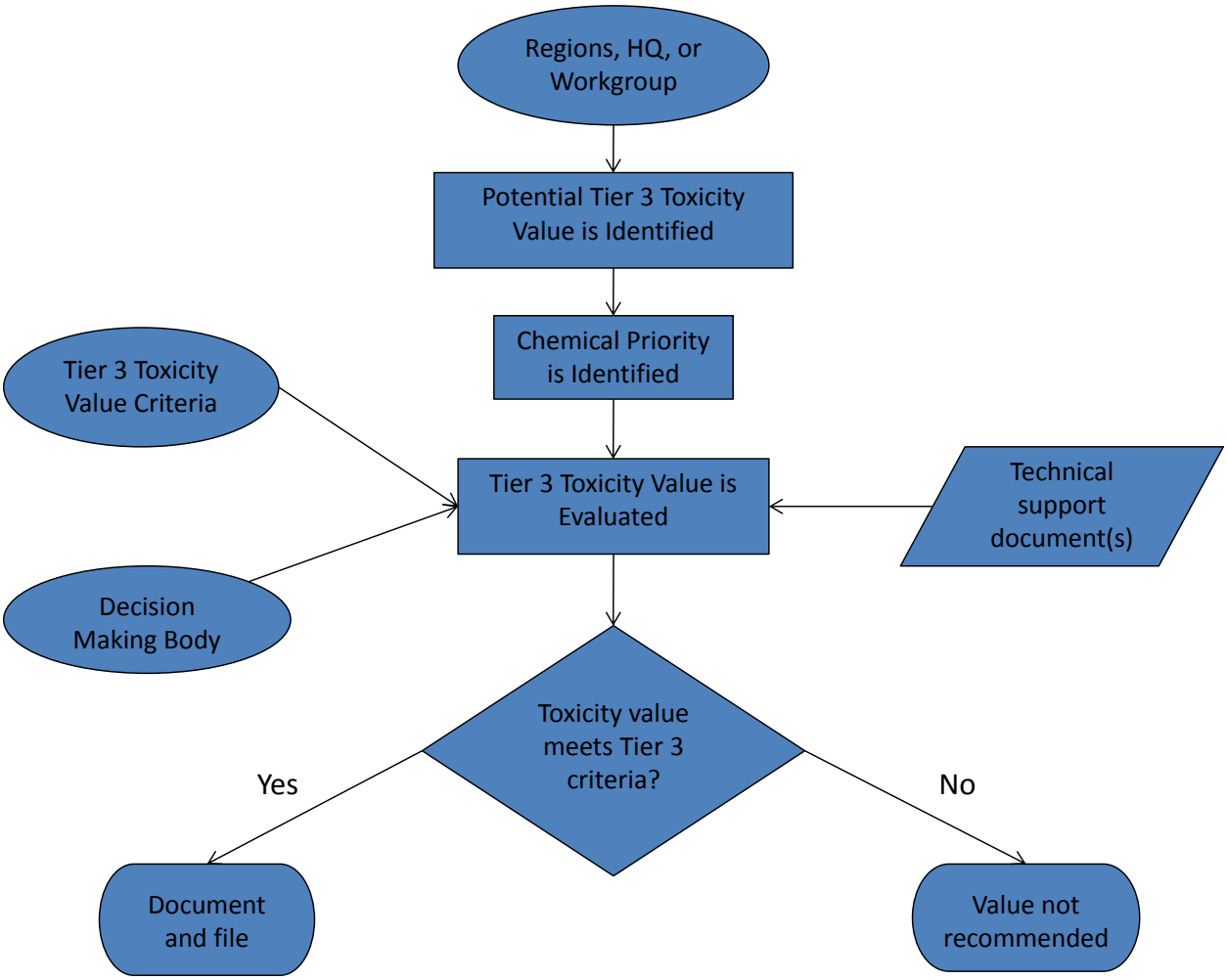
In April 2009, Region 7 provided guidance to the regional RCRA and Superfund programs on TCE toxicity values (see Appendix B). Specifically, the regional risk assessors recommended the use of the Cal/EPA cancer toxicity values and the NYSDOH non-cancer inhalation toxicity value, citing that they met the requirements of Tier 3 toxicity values (for example, had been peer-reviewed). With regards to the competing inhalation toxicity values, Region 7 provided rationale for selecting the NYSDOH value over the Cal/EPA REL.

During the spring 2011 RSL table update, the RSL workgroup provided a noncancer RfC for TCE based on the value derived by the NYSDOH (NYSDOH 2006).

5 Alternatives for Identifying, Evaluating, and Selecting, and Documenting Tier 3 Toxicity Values

As discussed in Section 1, the overall goal of the Regional Tier 3 Toxicity Value Workgroup is to establish a process that enhances the transparency and consistency of Tier 3 toxicity value identification, evaluation, selection, documentation, and communication. The steps in the overall process for selecting Tier 3 toxicity value are shown in Figure 1 below and described in the following sections. For this white paper, communication refers to the flow of information and overall coordination leading to selection and documentation of a Tier 3 toxicity value. Therefore, communication is part of the other steps and is not shown as a separate step. In addition, the priority of a chemical (regional or national interest) may play a significant role in determining the overall selection process and is therefore listed as a step in the selection process.

Figure 1. Tier 3 Toxicity Value Selection



5.1 Toxicity Value Identification

The regional risk assessors and RSL workgroup[9], through their routine work (site risk assessments and table updates), regularly encounter chemicals without Tier 1 and Tier 2 toxicity values. Thus, the identification of potential Tier 3 toxicity values has been largely their responsibility. This approach continues to be an option, however, this white paper also presents other potential avenues for identifying Tier 3 toxicity values. As an alternative to the regional risk assessors and RSL workgroup, a formal toxicity workgroup could be charged with identifying Tier 3 toxicity values, as well as other responsibilities (see Section 5.4.3.1). Although this responsibility is similar to the RSL workgroup, which looks at a broad range of chemicals, it is envisioned that the formal workgroup would look for potential Tier 3 toxicity values beyond the sources consulted by the RSL workgroup (for example, international sources). Furthermore, the workgroup's identification of potential Tier 3 toxicity could outpace the RSL workgroup because the former's sole focus would be to identify, evaluate, select, document, and communicate Tier 3 toxicity values.

If the responsibility for identifying potential Tier 3 toxicity values were assigned to a formal workgroup, several issues would need to be considered. First, the establishment of a new workgroup (assuming responsibilities are not subsumed within an existing workgroup) would require time and resources. In addition, it is uncertain whether the workload (new values being made available) would be sufficient to keep the group active. Furthermore, regional risk assessors and others will likely continue to search for Tier 3 toxicity values in their routine work (conducting risk assessments), leading to a duplication of effort. Thus, the value added of a formal workgroup is uncertain and would likely require the group to have multiple responsibilities to maintain member interest.

5.2 High vs. Low Priority

As a result of resource constraints, time, and other limitations and difficulties (such as potential controversy surrounding some chemicals), it is likely that no one alternative will be suitable as the sole means of evaluating and selecting all Tier 3 toxicity values. Thus, the priority of the chemical will likely dictate the entity that will evaluate and select a Tier 3 toxicity value. For instance, the examples provided in Section 4 clearly indicate that high-priority chemicals are elevated to headquarters.

The process for elevating Tier 3 toxicity values to headquarters and other entities (such as the RSL workgroup) has been rather informal in the past. If a more formalized and structured system of selecting Tier 3 toxicity values is implemented, a formal process for determining a chemical's priority may be needed, including criteria for distinguishing between those chemicals of low, medium, and high priority. This determination can be subjective and vary among the regions. Factors to consider in evaluating priority are described below. Of course, decision-making in regard to these criteria, especially a

[9] During the development of site-specific risk assessments, potentially responsible parties may identify Tier 3 toxicity values.

chemical's prevalence, may require coordination among the regions and headquarters, and the formal process may reinforce this requirement. Continued coordination and communication among potential decision-makers is also important so that elevation of a Tier 3 value to a headquarters or regional workgroup is efficient (chemicals are not elevated and then demoted).[10]

Below are a set of prioritization criteria that could be used to assist risk assessors, risk managers and others in assigning priority to a contaminant. Answering one of the questions below in the affirmative may not be sufficient to designate a contaminant as high priority. However, a preponderance of evidence should be adequate to support a high-priority designation. A contaminant with a high-priority designation would likely require a Tier 3 consultation by headquarters or a regional workgroup to ensure consistency across the Regions. Tier 3 contaminants that are not expected to drive health risks or remediation at a site, may be associated with mild health effects, are not encountered across multiple regions, or are not being considered for national rule making may be considered low priority. In this case, the decision to develop a Tier 3 toxicity value may be best left up to the individual region.[11]

Prioritization Criteria

- Does the contaminant have the potential to drive risks estimates and remediation at a site?

  Answering this question requires a minimum of toxicity information, such as a single subchronic or developmental study administered by the route of exposure expected to occur at the site. This information may be available from the database sources described in Section 2.1 or via an open literature search. If the answer to the question is yes, then the contaminant may be a candidate for a high-priority designation.

[10] Because regional risk assessors that submit potential Tier 3 toxicity values may have significant knowledge of the chemical, they may remain involved in the evaluation and selection process.

[11] In cases where the priority of a chemical falls somewhere in between high and low, best professional judgment should be used in deciding whether that chemical should be evaluated by headquarters or a regional workgroup (chemical evaluated as high priority) versus individual region (chemical evaluated as low priority). In cases of uncertainty, it is recommended a request be sent to the "Tier 3 Toxicity Value Steering Committee" (further discussed in Section 6.2), which would decide the priority designation and ultimately the proper action to be taken on a chemical-specific basis.

- Based on the available toxicity information and the concentration measured at the site, would the estimated human health effects be expected to be severe (irreversible damage affecting the function or viability of a receptor or target organ), moderate, or mild (transient, reversible effects)?

  Similar to the first question, answering this question requires a minimum of toxicity information. If the information suggests that the health effects to an individual would be severe or moderate, then the contaminant may be considered a high priority.

- Is the contaminant associated with a source or industry that is common across the region or multiple regions?

  The more prevalent a contaminant, especially across multiple regions, the more likely it is to receive a high-priority designation.

- Based on the chemical and physical properties of the contaminant, how likely is it that the remediation techniques used for the known risk drivers at the site would also remediate the contaminant in question?

  This question is not necessarily toxicological, but instead is a risk management question. If the remediation techniques being used at a site for the known risk drivers will also be successful in cleaning up the contaminant in question (based on what is known about the chemical and physical properties), it may not be efficient or necessary to delay a project while a Tier 3 toxicity value is being evaluated.

- Is the contaminant under consideration for rulemaking nationally?

  If EPA is considering the contaminant for rulemaking purposes, it should automatically be considered as a high-priority candidate. The best approach would be to ensure a consistent toxicity value across all regions and program offices because of the public visibility of the contaminant.

5.3 Toxicity Value Evaluation (Criteria for Selecting a Tier 3 Toxicity Value)

Per EPA risk assessment guidance and other relevant risk assessment publications, the ultimate goal of selecting a toxicity value for use in risk assessment is to select the most current and scientifically defensible value. With regard to the selection of Tier 3 toxicity values, this value is selected by applying a combination of the general guidance principles discussed in Section 2.2 and the recommendations and preferences discussed in EPA and non-EPA risk assessment guidance (see Section 3). The following sections outline a proposed process that could be used to evaluate and select Tier 3 toxicity values.

5.3.1 Basic Requirements for Consideration as a Tier 3 Values

After a potential Tier 3 toxicity value has been identified, the first step is to determine whether that value meets the basic requirements of a Tier 3 value. As discussed in OSWER's 2003 Toxicity Value Hierarchy, three key factors for a toxicity value to be considered in the selection of a scientifically defensible Tier 3 value are that the value is peer-reviewed, publically available, and that the source is transparent about the methods and procedures used to develop the value. These same factors are also discussed in several of the seven preferences provided in the ECOS paper and echoed in other EPA guidance (such as RAGS Part F). Despite the requirements implied in the aforementioned documents, the level of peer-review is not specified. Thus, per EPA's peer review policy, decision-makers (the entity evaluating a potential Tier 3 toxicity value) have to consider whether the level of peer review matches the significance of the chemical. Availability and transparency are more straightforward. However, decision-makers have to determine, for example, whether an Internet posting of a summary file of a toxicological assessment (instead of the entire toxicological file) meets the availability and transparency criteria unless an internet link to the entire file is provided.

It is also important to evaluate the quality and usability of the underlying data supporting the potential Tier 3 value. Although a precise level of data quality and usability has not been defined, some toxicity values may not be of suitable quality or usability even though they have been peer-reviewed and are publically available. For example, some toxicity values may be based on route-to-route extrapolations of peer-reviewed values. Therefore, this step may focus on major deficiencies that would preclude use of a potential Tier 3 toxicity value. When competing Tier 3 values are available, this step may also indicate the preferred value.

5.3.2 Tier 3 Toxicity Value Critical Review

Section 2.2 introduced the general guiding principles for evaluating the quality and usability of Tier 3 toxicity values. Specifically:

(1) The quality and usability of the animal and human studies used to derive the toxicity values,
(2) How adverse and critical effects are defined, and
(3) The methodologies used to derive the cancer or noncancer toxicity value.

This white paper proposes the use of the guiding principles to conduct a more critical evaluation of the potential Tier 3 toxicity value.

5.3.2.1 Quality and Usability of Toxicity Testing Studies

There are a number of factors to consider in evaluating whether an animal or human toxicity testing study should be used in developing a toxicity value. The first is whether the study was conducted per the appropriate testing guidelines for the regulatory agency. For EPA, these guidelines are the harmonized test guidelines discussed in Section 3.1.5. Other guidelines include the Good Laboratory Practice (GLP) and the Food and Drug Administration (FDA) and Organization for Economic Co-Operation and Development (OECD) guidelines. Per these guidelines and other relevant documents (see for example EPA 1994, 2002, 2005, and 2008), factors to consider in the critical evaluation of the quality and usability of toxicity testing studies include:

- What is the route of administration of test material?
- What is the animal species tested?
- What is the dose duration (acute, sub-chronic, or chronic)?
- Is the apparent difference treatment-related?
- Is the effect dose-dependent?
- Is the effect biologically significant (as opposed to statistically significant)?
- Are the effects seen in multiple species, strains, or both sexes?
- Are the results relevant to humans?
- Were the study results interpreted properly?
- Is supporting evidence such as physiologically based pharmacokinetic modeling, metabolism studies, or structure activity relationship studies available?

Note that both the individual studies and the database of human and animal toxicity testing studies can be ranked as having low, medium, or high confidence based on an evaluation of these factors (see Section 5.3.3).

5.3.2.2 Defining Adverse and Critical Effects

Another critical element in the evaluation of a toxicity value is how adverse and critical effects are defined. An adverse effect is defined by EPA as the biochemical change, functional impairment, or pathological lesion that impairs performance and reduces the ability of an organism to respond to additional challenge (http://www.epa.gov/iris/help_gloss.htm). The lowest dose level at which an adverse effect occurs is defined as the critical effect level and is typically expressed as the LOAEL or lowest observable effect level (LOEL). A dose level at which there are no statistically or biologically significant increases in the frequency or severity of any effect between the exposed population and its appropriate control is the NOAEL. The critical effect level can also be determined using a benchmark dose approach or categorical regression. Thus, it is useful to consider the following in checking a study:

- Were the study results interpreted properly?
- Was the effect identified as adverse truly a biologically significant adverse effect?
- Is the adverse effect consistent with what is known about the chemical and the other studies in the database?

It is also important that the critical effect level be adjusted to the dose metric of interest (for example, parts per million [ppm] in food to milligrams per kilogram per day [mg/kg-day] for the oral route), for duration of exposure (such as from periodic to daily or continuous exposure), and scaled from an animal to a human equivalent body weight or concentration. Without these adjustments, it is not possible to compare effect levels on an equivalent basis. A study that might appear to have the lowest point of departure on first glance may not when the correct dosimetric adjustments are made. The critical effect (NOAEL or LOAEL, point of departure if using a benchmark dose approach, and categorical regression) is used as the starting point for calculating toxicity reference values for threshold toxicants.

5.3.2.3 Derivation of Noncancer and Cancer Toxicity Values

As mentioned in Section 2.2.3, the methodologies used to calculate toxicity values are typically specific to the regulatory agency involved. Understanding their differences and similarities are also useful when potential Tier 3 toxicity values and competing values are evaluated. EPA, for example, uses an RfD approach to calculate toxicity values for threshold toxicants administered by the oral route of exposure. An RfC is estimated for the inhalation route. This approach determines the critical effect level in the principal study or studies and applies uncertainty factors to account for:

(1) Variation in susceptibility among the members of the human population (inter-individual or intraspecies variability);
(2) Uncertainty in extrapolating animal data to humans (interspecies uncertainty);
(3) Uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (extrapolating from subchronic to chronic exposure);
(4) Uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and
(5) Uncertainty associated with extrapolation when the database is incomplete.

The default for each of these uncertainty factors is a value of 10. The exact value (10, 3, or 1) of the uncertainty factor selected may depend on the quality of the studies available, the extent of the database, and scientific judgment. Some factors to consider when the default factor of 10 is replaced with a lesser value are chemical-specific toxicokinetic or toxicodynamic data, the severity of the effect, the slope of the dose-response curve, and the presence of developmental and reproductive studies. For a more in-depth discussion, please see EPA's report titled *A Review of the Reference Dose and Reference Concentration Process* (EPA 2002). When a toxicity value is evaluated from the ATSDR database (or any other state, federal, or international regulatory program), the application and interpretation of uncertainty factors will differ from EPA's approach. Understanding these differences is important because the application of uncertainty factors may alter the final toxicity value by 1 to 5 orders of magnitude.

Some regulatory agencies, such as Health Canada, may use a margin of exposure (MOE) approach. Instead of reducing the critical effect level by a number of uncertainty factors, the MOE approach compares site-specific exposures directly with the critical effect level. The resulting ratio is then evaluated to determine if there is an adequate margin of safety.

For carcinogenic substances, qualitative descriptors are often provided on the likelihood of a chemical agent to cause cancer in humans. EPA currently uses five recommended standard hazard descriptors: "Carcinogenic to Humans," "Likely to Be Carcinogenic to Humans," "Suggestive Evidence of Carcinogenic Potential," "Inadequate Information to Assess Carcinogenic Potential," and "Not Likely to Be Carcinogenic to Humans" (EPA 2005). Different regulatory agencies and health organizations will use different qualitative descriptors. For example, IARC classifies carcinogens as Group 1 (carcinogenic to humans), Group 2A (probably carcinogenic to humans), Group 2B (possibly carcinogenic to humans), Group 3 (not classifiable as to its carcinogenicity to humans) and Group 4 (probably not carcinogenic to humans).

Some regulatory agencies and health organizations will quantify the dose-response assessment of carcinogens, while some may simply regulate a toxicant if it is deemed to be a possible carcinogen. EPA provides a quantitative estimate of the dose-response relationship by fitting the cancer bioassay data within the range of observation and deriving a point of departure (the lowest data point adequately supported by the data). If the mode of action data supports nonlinearity, an RfD or RfC is calculated from the point of departure. If the mode of action data indicate the dose response curve is expected to have a linear component below the point of departure, a linear extrapolation below the point of departure is used. The slope of this line is the slope factor. Agencies may differ on their interpretation of whether the dose response curve is linear or non-linear below the point of departure, resulting in different calculations of a cancer toxicity values.

Other regulatory agencies and health organizations, particularly in Europe and Asia (World Health Organization [WHO], International Programme on Chemical Safety [IPCS], and International Life Science Institute Europe) support a MOE approach for assessing carcinogens, regardless of the mode of action. The MOE approach compares the margin between a dose or an exposure causing cancer in animals or humans (for example, the point of departure) with the estimated human exposure to that substance. The resulting ratio is then evaluated to determine if there is an adequate margin of safety.

5.3.3 Tier 3 Toxicity Value Confidence

This white paper proposes that the confidence in a particular Tier 3 toxicity value could be ranked as low, medium, or high as part of a critical review. Ranking the level of confidence could be useful for determining the relative appropriateness of using Tier 3 toxicity value in various steps of the human health risk assessment process, as well as assisting with the selection of a value when competing values are available. A value that receives a "low" confidence ranking may be helpful during the initial screening process (for example, when determining if an analyte is a chemical of concern and should be carried forward into the baseline risk assessment process); however, a toxicity value with a "low" confidence ranking may be not be suitable for use in the baseline risk assessment or development of preliminary remediation goals because of limitations in this value. For CERCLA and RCRA processes that undergo more critical examination, a toxicity value with a "medium" or "high" confidence ranking would be more appropriate.

Below are some examples using the guiding principles mentioned above and discussed in Section 2.2 in applying confidence rankings to toxicity values.

The first element is the quality and usability of the animal and human studies used to derive the toxicity values. If only one animal species is tested for a subchronic period of exposure using only one dose level by a route of administration not consistent with the exposure route being evaluated at a CERCLA or RCRA site, the confidence in the toxicity value would likely be considered to be "low." The value could be used during the screening process, but would likely be inappropriate for a baseline risk assessment. If the contamination levels at a CERCLA or RCRA site exceed screening levels based on a Tier 3 value with low confidence, then the risk assessor has several choices. One choice would be to move to a qualitative assessment of the contaminant during the baseline risk assessment. Another choice would be to submit the contaminant to the STSC for a more thorough evaluation and a second opinion on the usability of the database and toxicity value. A third option would be to retain the Tier 3 value in the baseline risk assessment and be prepared to defend the scientific credibility of the value as part of the uncertainty assessment.

The second element is how the adverse and critical effects are defined. If the adverse effect is consistent with the definition provided in EPA's IRIS database (http://www.epa.gov/iris/help_gloss.htm) and is both biologically and statistically significant, then a ranking of "medium" or "high" may be assigned.

The third element is an examination of the methodology used to derive the quantitative toxicity value from the defined adverse effect. If the methodology is consistent with the cancer or noncancer methodology described in EPA's IRIS database (http://www.epa.gov/iris/) or adequately accounts for uncertainty and variability within susceptible populations, then a confidence of "medium" or "high" can be assigned. The overall ranking from these elements will be useful in determining where in the CERCLA or RCRA process the toxicity value would be most appropriate to use.

5.4 Options for Tier 3 Toxicity Value Consultations

There are several possible options for the types of decision-making bodies that could provide Tier 3 toxicity value consultations. Some of the possible options, which are discussed in the following sections, include forming or consulting an Action Development Process Workgroup; forming or consulting a headquarters or regional workgroup, or having individual regions evaluate and select values. In addition, the range of potential options is further expanded when considering the scope of consultation. For example, the requestor could be responsible for performing the evaluation and the consultation workgroup provides only a brief review and approval. Alternatively, the consultation workgroup could be charged with conducting the full evaluation of the potential Tier 3 toxicity value. Section 4.1.1.2 provides some examples of how this has been done previously.

One factor that should be considered in making the decision is the potential impact of the Tier 3 toxicity value under consideration and whether it should be considered influential scientific information. Consistent with EPA's Information Quality Guidelines (http://www.epa.gov/QUALITY/informationguidelines/) and the Office Management and Budgets Peer Review Bulletin (http://www.whitehouse.gov/sites/default/files/omb/memoranda/fy2005/m05-03.pdf), influential scientific information is that which the agency reasonably can determine will have or does have a clear and substantial impact on important public policies or private sector decisions. Influential scientific information is expected to maximize quality, objectivity, utility, and integrity.

In addition to the visibility and priority of the chemical, there are several other key issues that will need to be considered in establishing processes for developing Tier 3 toxicity values. These issues include, but are not limited to, the overall coordination and process for requesting consultations, contract support, and documentation. Additional discussion on these issues is provided in the following "options" sections and in Section 5.5

5.4.1 Action Development Process Workgroup

The Action Development Process (ADP) is the Agency's accepted method for producing high-quality actions, such as regulations, policies, and risk assessments. It ensures that EPA uses the best available information to support its actions and that scientific, economic, and policy issues are adequately coordinated with the various stages of action development. More information is available on the Office of Policy, Economics & Innovation's (OPEI) Intranet site http://intranet.epa.gov/adplibrary. Tier 3 toxicity values that would be considered influential scientific information should generally be developed through the ADP. Typically, this process would be initiated by OSWER. Briefly, the process begins with a tiering by the Regulatory Steering Committee. There are three possible tiers related to the level of senior level management involvement and the extent of cross-agency influence: Tier 1 actions are signed by the Administrator and typically have broad cross-agency influence, Tier 2 actions are signed by Assistant Administrators and typically have some cross-agency influence, and Tier 3 actions are typically signed by Office Directors and generally have limited cross-agency influence. Development of Tier 3 toxicity values using the ADP would typically be considered a Tier 3 action. The ADP has a number of prescribed steps that are required for all Tier 1 and Tier 2 actions; Tier 3 actions can be less formal, but typically include Office of Management and Budget (OMB)-led interagency review.

5.4.2 Headquarters Consultation

Headquarters, including offices within OSWER and ORD, have advised regions in the past on the use of Tier 3 toxicity values. Typically, regions have submitted requests to OSWER, which has responded with its recommendations. These requests have included consultations on chromium (VI), PCE, PFOA, and PFOS. Generally, these consultations were led by OSWER, but also included input from ORD. In addition, consultations were often coordinated among various offices within OSWER, including the

science advisor, OSRTI, and OEM. The scope of these consultations also varied. Whereas much of the toxicity value evaluation for chromium (VI) was performed by Region 2, most of the toxicity value evaluation for PFOS and PFOAs was performed by OSWER and consulting programs.

This approach remains a viable method for evaluating and selecting Tier 3 toxicity values, especially for high-priority chemicals where consistency and headquarters support are paramount. The headquarters consultation could continue to be performed on an "informal" basis, or a more formalized consultation process could be adopted in the future. Under the informal process, regions would continue to send requests to any of the multiple risk assessment and toxicology program contacts in OSWER including, but not limited, to OSRTI, OEM, or PARMS. Those offices would be responsible for establishing the consultation workgroup. Under the formal consultation process, it is envisioned that all consultations would be led and authored by a designated office within OSWER (such as OSRTI) and include a small group of technical experts and representatives from various programs, regions, and laboratories (such as ORD).

Regardless of whether an informal or formal approach is taken, several key factors will need to be considered for headquarters consultations. First, headquarters may need to establish a point of contact for consultations to coordinate reviews. In other words, headquarters may need to designate an individual or group of individuals who could receive Tier 3 consultation requests. Likewise, to eliminate redundancy (same requests from multiple regions) and improve the communication of toxicological information, the regional risk assessors may need to establish a process for submitting requests. The OSWER Human Health Regional Risk Assessors Forum (OH2R2AF) and OH2R2AF toxicity workgroup could fulfill this role. Furthermore, depending on the scope of the consult and the resource and time constraints, contract support may be necessary to assist headquarters with the collection, evaluation, coordination, and documentation of information pertaining to the consult.

There are several benefits to using headquarters consultations. Because of its role in providing guidance and policy to the regions, and centralized location within the organization, headquarters-based consultations, which may be provided by a designated office in headquarters, are more likely to maintain a consistent approach in the application of review criteria compared with other alternatives that may rely on multiple entities to provide consults. Furthermore, as a result of its position of authority, headquarters consultations also add "greater weight and credibility" to a Tier 3 value. Headquarters consultations are also more likely to include involvement from other program offices at the national level (e.g.,OPP), which may add greater credibility to and support for a particular Tier 3 toxicity value.

Despite the benefits associated with headquarters consultations, there are some potential challenges. The biggest challenge pertains to the perception that headquarters is setting policy. There are specific requirements for headquarters for the development of guidance and policy (such as interagency and OMB review). Although consultations are not equivalent to agency guidance or policy, the perception that headquarters is setting policy, especially among high-priority chemicals, could stall efforts. Consultations could be delayed if the program office has to defend perceptions of setting policy to

management and others. Subject matter experts from other program offices may also be reluctant to provide input if it appears they are setting policy for their particular program.

Another potential challenge with this alternative is that it may not be well suited to handle low-priority chemicals. Headquarters will tend to have the greatest interest in chemicals that have significant affects on risk management decisions or that are found in numerous regions. Thus, headquarters could exhaust its resources and time in high-priority chemicals and have little time to complete consults on low-priority chemicals. Consults would also have to compete with other headquarters projects and priorities. Therefore, headquarters may have difficulties in getting adequate technical support from subject matter experts for the consult.

5.4.3 Regional Workgroup

Another method for evaluating and selecting a Tier 3 toxicity value is through the use of a regional workgroup. The regional workgroup could be established as a formal regional workgroup or as an *ad hoc* work group consisting of subject matter experts with expertise relevant to the chemicals being evaluated. These workgroups would be led by and generally consist of regional risk assessors and toxicologists.[12] Headquarters risk assessors and toxicologists could be involved, but serve more or less as advisors. It is anticipated that the regional workgroup would primarily focus on low- to medium-priority chemicals, but may provide guidance on the high-priority chemicals that would not be considered influential scientific information.

There are two existing regional workgroups that could evaluate and select Tier 3 toxicity values. They include the RSL workgroup and the newly formed OH2R2AF toxicity workgroup. Because these workgroups' primary roles are to maintain the RSL Table and to address overall toxicity value needs and issues within the regions, a separate workgroup focused on Tier 3 toxicity values may be a viable alternative. However, under this alternative, such a workgroup may require coordination and direction from an overarching workgroup, such as the RSL workgroup and OH2R2AF toxicity workgroup (see below).

The role of these workgroups could vary significantly. The regional workgroup's role could be limited to advising regions that have identified a potential Tier 3 toxicity value, which may include evaluating the toxicity value and providing recommendations regarding the candidate value. In addition to providing consultations, the regional workgroup's role could be expanded to identifying, reviewing, and providing recommendations on Tier 3 toxicity values independent of requests from regions. This latter role would likely require formation of a formal workgroup.

[12] Because regional risk assessors that submit potential Tier 3 toxicity values may have significant knowledge of the chemical, they may remain involved in the evaluation and selection process as a regional workgroup member or advisor.

Although the level of effort of these workgroups will depend on their scope and the amount of toxicological information available for a given compound, contract support may be necessary. Under the consultation role, contract support would likely be limited and vary according to the chemical. The requestor of the consult may perform the bulk of the evaluation. However, contract support may be necessary for a workgroup that is routinely involved in identifying, reviewing, and providing recommendations on Tier 3 toxicity values independent of requests.

5.4.3.1 Formal Regional Workgroup

A formal regional workgroup, presumably under the auspices of the OH2R2AF, could play a dual role as a consulting workgroup and workgroup that actively identifies, reviews, and makes recommendations on Tier 3 toxicity values. This workgroup would generally be composed of and led by regional staff. Its membership could be fixed or consist of a small group of permanent members whereby subject matter experts fill temporary membership positions on a chemical-specific basis. Likely roles for this workgroup, in addition to the those listed above, may include evaluating existing Tier 3 toxicity values provided in the RSL table and periodically reviewing Tier 3 sources for new or updated toxicity values. Additionally, this group could derive new toxicity values. However, the roles involving periodic review of existing Tier 3 toxicity values in the RSL table and the derivation of toxicity values fall outside the scope of this white paper.

There are several strengths and limitations of establishing a formal regional workgroup. It is envisioned that a formal regional workgroup would select a core membership, structure it's organization (perhaps by developing a charter), and schedule regular meetings. Such a group could be more easily tracked in terms of agenda and progress, and a formal structure would make the workgroup easier to manage and have clearer expectations. In addition, both the workgroup and its members would be more visible to headquarters and the regions and provide greater credibility to the selection of a toxicity value. In addition, it is likely that a formal workgroup would more likely maintain a consistent process (for example, in application of review criteria) for evaluating and recommending new Tier 3 toxicity values. However, if the workgroup is formalized and core membership is fixed, the workgroup may lack expertise and/or fail to reach out to others with expertise in a particular chemical or toxicity value development (Ibid). Lack of subject matter expertise would limit the scientific credibility and usability of the toxicity value, which is the end product. Furthermore, the workload may not require regularly scheduled meetings, potential resulting in loss of focus and interest among the workgroup members and less than satisfactory work products.

5.4.3.2 Ad Hoc Regional Workgroups

Regional workgroups, under the direction of a coordinating committee (such as the OH2R2AF toxicity workgroup), could also be formed on an as needed basis to provide consultation on the use of Tier 3 toxicity values. The coordinating committee would receive Tier 3 consultation requests and be charged with staffing an *ad hoc* regional workgroup with regional risk assessors and toxicologists with subject matter expertise relevant to the chemical in question. The group's charge would also include

establishing a workgroup chair (a regional risk assessor or toxicologist) who would be responsible for leading the consultation and documenting the consult (drafting the memorandum). ORD and headquarters could also participate on these workgroups, especially if the regions are lacking subject matter expertise. Given that this workgroup would be formed on an as-needed basis, it is not likely that it will be evaluating and providing recommendations on existing Tier 3 toxicity values or periodically reviewing Tier 3 sources for new or updated toxicity values. Those roles would likely be retained by existing workgroups, such as the RSL table workgroup and the regional risk assessors.

Regardless of whether the coordinating responsibilities fall within a new or existing workgroup, the coordinating committee will have to put itself into position to receive Tier 3 toxicity value consultation requests and assign workgroups in a timely and efficient manner. Thus, the coordinating committee will have to maintain visibility among the regional risk assessors so that it is known to whom requests should be sent. The coordinating committee will also have to maintain a list of subject matter experts to staff the workgroups. Maintaining this list would likely require the coordinating committee to reach out to the regional toxicologists and risk assessors and possibly others in headquarters to determine whether they can and would participate on the workgroup should their expertise be needed.

There are several strengths and benefits with the use of *ad hoc* regional workgroups. Unlike the formal regional workgroup, which is limited to the expertise of its members, an *ad hoc* regional workgroup could be staffed with members who already have expertise on a particular chemical or chemical group. This approach to staffing could decrease the amount of time it takes to provide a consult and provide greater credibility/weight to the consult. In addition, *ad hoc* regional workgroups may also better champion the needs and priority for a Tier 3 toxicity value on a chemical that has a region-specific or limited geographic distribution in the environment. Unlike a formal workgroup or headquarters consult, an *ad hoc* workgroup could be composed of members who all have an interest in the chemical in question and completing a consult. However, this composition also could bias the consult. An *ad hoc* regional workgroup would also be focused on one particular task and less likely to be distracted from competing priorities, thereby decreasing the amount of time for a consultation and potentially improving the quality of the review. Furthermore, assuming the *ad hoc* workgroups are well-coordinated, this option would likely maximize available resource by spreading the responsibilities among many versus a few.

Along with the strengths and benefits of an ad hoc workgroup, this option has its limitations and challenges. Several of these limitations and challenges could stem from the coordinating committee. As indicated above, coordination is a critical component of this option. Thus, this option would lack effectiveness if the coordinating committee is poorly organized and managed. In addition, the formation and staffing of an *ad hoc* work group for each new chemical under consideration may be cumbersome and time consuming for the coordinating committee. Because the *ad hoc* regional workgroup will likely be coordinated by a regional workgroup, it may also suffer from lack of membership or input from EPA in headquarters and ORD (such as OSWER risk assessor or NCEA scientist). From a planning perspective, an *ad hoc* workgroup may make it difficult to staff workgroups

with subject matter experts from ORD or headquarters on an as-needed basis, let alone regional subject matter experts.

Although this option allows for the tailoring of a workgroup around a particular expertise, multiple *ad hoc* workgroups can pose some additional challenges. The use of the *ad hoc* approach could reduce the likelihood that a consistent process would be maintained for evaluating and recommending new Tier 3 toxicity values. One workgroup may apply evaluation criteria differently than another group. Thus, additional guidance and direction on the use of criteria may be needed to improve consistency. Furthermore, an *ad hoc* workgroup needs a mandate or direction that will not ultimately put it at odds with another Tier 3 workgroup (clarity of relationship between *ad hoc* workgroups and the RSL Workgroup).

5.4.4 Joint Headquarters/Regional Workgroup

Risk assessors and toxicologists in the regions and headquarters (OSWER and ORD) have had a long history in working together in developing and implementing risk assessment guidance and toxicological assessments pertaining to Superfund and RCRA. In recent years, additional efforts (such as OH2R2AF) have been undertaken to enhance communication between headquarters and regional Superfund and RCRA risk assessors. A joint workgroup consisting of regional and headquarters risk assessors and toxicologists could be established to provide consults on Tier 3 toxicity values because many of these efforts involve workgroups consisting of a mixture of regional headquarters representatives. This option is nearly identical to the regional workgroup option discussed in Section 5.4.3, except that this workgroup could be led by either a headquarters or a regional risk assessor and would have to include members from both regions and headquarters. Note that the regional workgroups do not necessarily have to include headquarters representatives. Based on headquarters' greater role in such a workgroup, it is likely that this workgroup could work on medium- to high-priority chemicals.

The joint regional and headquarters workgroup also shares many of the same strengths and limitations that the regional workgroup option may offer. In addition, this option allows for more coordination between headquarters and the regions, which could provide greater transparency and credibility to Tier 3 toxicity value consultations over a regional workgroup. A greater role for headquarters may also increase the likelihood that subject matter experts from headquarters will be involved in providing the consult. However, the share of power between the regional risk assessors and headquarters could limit the joint workgroup's effectiveness. Competing interests (completing a site risk assessment versus setting policy) could slow the workgroup activity.

5.4.5 Individual Regions

Under this approach, individual regions would continue to use their current methods for identifying and selecting Tier 3 toxicity values. With the exception of the RSL table (and its predecessors), which have provided recommendations on Tier 3 values, regions have already been largely responsible for identifying Tier 3 toxicity values and providing guidance to responsible parties, states, and other entities.

However, regions have consulted headquarters and other regions for high-priority chemicals (such as chromium VI) or chemicals commonly found at sites. Therefore, this approach is anticipated for use with low- to medium-priority chemicals. The development of Tier 3 toxicity values for high-priority chemicals will likely need the input from a regional workgroup or headquarters, especially risk-driving chemicals. As stated in the 2003 OSWER toxicity value hierarchy, "Consultation with the STSC or headquarters program office is recommended regarding the use of the Tier 3 values for Superfund response decisions when the contaminant appears to be a risk driver for the site" (EPA 2003).

There are several strengths with the individual regions approach. To begin with, a relatively quick turnaround time is associated with the approach. Rather than waiting for a response from headquarters or a workgroup, decisions can be made within the region which assists in a quick turnaround time. Following the individual regions approach allows regions to retain control of the selection of Tier 3 values. Furthermore, it allows for development of a more complete and thorough risk assessment, which limits the possibility of underestimating risks.

As with the previous approaches, there are several limitations to individual regions evaluating and selecting Tier 3 values. For instance, there is potential for lack of transparency and consistency with regard to decision making. At times, information is not shared outside of the region, or even within the region (between the programs). The lack of transparency (or information sharing) creates a problem when different Tier 3 values are recommended by different regions. Because the criteria for selecting a Tier 3 value do not specify the level of peer review, it is possible that several values could be chosen for a chemical by different regions. The credibility of such a toxicity value is more likely to be questioned by a responsible party (RP), resulting in a greater chance of challenge, especially for risk-driving chemicals, which draw an additional level of scrutiny. Since the credibility of regionally selected Tier 3 values may vary greatly, it is important to consult experts who can identify limitations of published values. However, by definition, the regional approach discourages seeking expert advice across regions in decision making. This lack of a cross-regional approach contributes to the limitations since the toxicological expertise of the decision-maker within each region may vary extensively. Finally, this approach does not address high-priority chemicals, which may need to be sent to headquarters for a decision. It should also be noted that although it is possible for individual regions to identify available Tier 3 toxicity values for certain chemicals of use and interest, regions often lack appropriate resources and expertise to adequately evaluate and select a Tier 3 value. In such instances, assistance from headquarters and other groups are often necessary.

5.5 Documentation

As noted in previous sections, transparency is a necessary component of a Tier 3 toxicity value. Therefore, identification and selection of a Tier 3 toxicity value by EPA risk assessors must continue to be transparent. Transparency includes documenting the decisions and recommendations regarding the selection of a Tier 3 toxicity value and its supporting toxicological assessments and making these documents available to the public. The following sections discuss potential methods for documenting

and distributing decision documents and alternatives (repositories) for warehousing decision documents and supporting documentation (for example, toxicological assessments).

5.5.1 Decision Documents and Distribution

As shown in Section 4.2 and Appendix B, consults and recommendations on Tier 3 toxicity values have taken the form of e-mails, formal memoranda, or listings in a table (the RSL table) and the level of detail regarding the support of these values has differed. Although future consults and recommendations may take several forms, development of a process for selecting a Tier 3 toxicity value may need to consider the level of formality needed in consults and recommendations and the type of information to be included in the consult or recommendation. For example, formal signed memoranda may offer more of an authoritative voice than informal e-mails. With regards to the types of information to be provided in consults or recommendations, it may include, but may not be limited to, the following:

- Transparency, peer-review, and availability criteria met,
- Summary of the underlying studies,
- Methods for toxicity value derivation,
- Uncertainty Factors (RfCs and RfDs),
- Carcinogenic mechanism of action (MOA) (if available),
- Target organ and critical effect, and
- Confidence in toxicity value.

Also, before decision documents and toxicological assessments are warehoused (see Section 5.5.2), timely notification of such decisions may be of interest to regional risk assessors. Regional risk assessors have expressed interest in what other regions are doing to avoid re-inventing the wheel or being inconsistent. However, notification does not necessarily mean that all regional decisions have to be distributed outside of the region. There is the potential for inconsistency or that the value is not used in a risk assessment because it may take some time between a decision on a Tier 3 toxicity value and its use, for example, upload into a database. Thus, a process for selecting a Tier 3 toxicity value, should consider a method for notifying regional risk assessors of any decisions regarding a Tier 3 toxicity value. Typically, e-mails have been an effective tool for distributing this type of information and have been the case with most headquarters consults. However, these e-mails have often been distributed from the requesting region and may not have been distributed to all regional risk assessors. In addition, e-mails may not always be read by all recipients. Other potential methods that could expand the risk assessor audience may include broadcasts in the OH2R2AF newsletter or during the OH2R2AF calls. Finally, some consideration should be given to how this information will be shared with other audiences (such as state risk assessors before they are sent to a repository.

5.5.2 Repositories

Decision documents and supporting documentation (in this case, toxicological assessments) behind a Tier 3 toxicity value must be stored and available for retrieval by risk assessors, risk managers, and the public. The following sections discuss potential alternatives for warehousing this information. In addition, the potential repositories discussed below may not apply to all situations because individual regions may continue to develop their own Tier 3 values internally. However, it is expected that the regions that develop their own values would be responsible for storing their decision documents and supporting documentation, unless they plan to distribute the values beyond their region.

In addition, on-line repositories will require storage space, routine maintenance, and a point of contact (for adding or revising a Tier 3 toxicity value). Although it is not the intent of this document to discuss these issues in depth, costs and resources associated with storage and maintenance of decision documents and supporting documentation will have to be considered and evaluated. Given these potential constraints and other considerations (duplication of effort), links to non-EPA websites that contain the toxicological assessments may be a viable alternative to storing the toxicological assessments on EPA's website.

5.5.2.1 PPRTV Assessments Electronic Library

The PPRTV Assessments Electronic Library is a potential repository for Tier 3 toxicity values. The PPRTV electronic library, which has recently become publically available, is administered by OSRTI and maintained by Oak Ridge National Laboratory under an interagency agreement. Notwithstanding contractual arrangements, an additional menu could be added to the PPRTV electronic library to house Tier 3 toxicity values. Similar to the PPRTVs, the menu could contain a list of all chemicals with Tier 3 toxicity values. When a given chemical is selected, the user would be sent to a page that contains the Tier 3 toxicity values, decision documents, and the toxicological assessments.

5.5.2.2 Superfund Health Risk Technical Support Center (STSC)

The STSC provides technical support to EPA program and regional offices in the area of human health risk assessment, such as the development of PPRTV assessments and scientific consultations. In years past, the STSC has served as a repository for health risk assessment documents, such as hard copies of HEAST derivation support documents. For these reasons, the STSC could serve as a repository for Tier 3 consults, recommendations, and supporting documentation. However, , STSC may not be a viable alternative for storing recommendations on non-EPA toxicity values and their technical support documents because the STSC develops PPRTVs and provides support for interpreting EPA publications and guidance.

5.5.2.3 RSL Table Website

The RSL table website, which is posted by Regions 3, 6, and 9, is another potential repository for Tier 3 toxicity values. The RSL table website appears to be a logical choice as a potential repository for supporting documentation because the RSL table is typically the first EPA document to post Tier 3 toxicity values. The user's guide and supporting tables could be expanded to include a page that contains the decision documents. This page could also provide the toxicological assessments or links to the toxicological assessment on non-EPA websites. Because the RSL summary table already contains fields for toxicity values, a separate location listing Tier 3 toxicity values would not be necessary. Furthermore, although the RSL table is not an original source of toxicity values, it often serves as the initial destination for Superfund and RCRA risk assessors seeking the most current toxicity values used by EPA. Thus, use of the RSL table as a repository location for Tier 3 toxicity values could decrease the number of locations risk assessors would have to search for toxicity values. However, as noted above, the RSL table and its supporting documentation (such as the User's Guide) are posted on the Region 3, 6, and 9 websites. While only one Region (Region 3) stores the files (the other two provide links only), this option would require approval and coordination with the Regions' IT and risk assessment staff and management. Note that it is unknown whether the regions currently storing the RSL tables are capable of and willing to take on this additional duty as doing so requires additional storage and resources. Furthermore, the layout of a Tier 3 toxicity value repository would be subject to the individual region's formatting preferences.

5.5.2.4 Tier 3 Toxicity Value Database

Although no such database exists at present, an on-line database strictly for Tier 3 values could be developed. This database would be strictly for Tier 3 toxicity values and, like the IRIS and PPRTV databases, its location will be readily identifiable as a source for recommended Tier 3 toxicity values. It is envisioned that it would be formatted similar to the PPRTV library with drop-down menus. Although such a site would provide a centralized and distinct location for Tier 3 toxicity values, it may require a significant amount of additional money and resources to design and maintain compared with the use of an existing on-line repository.

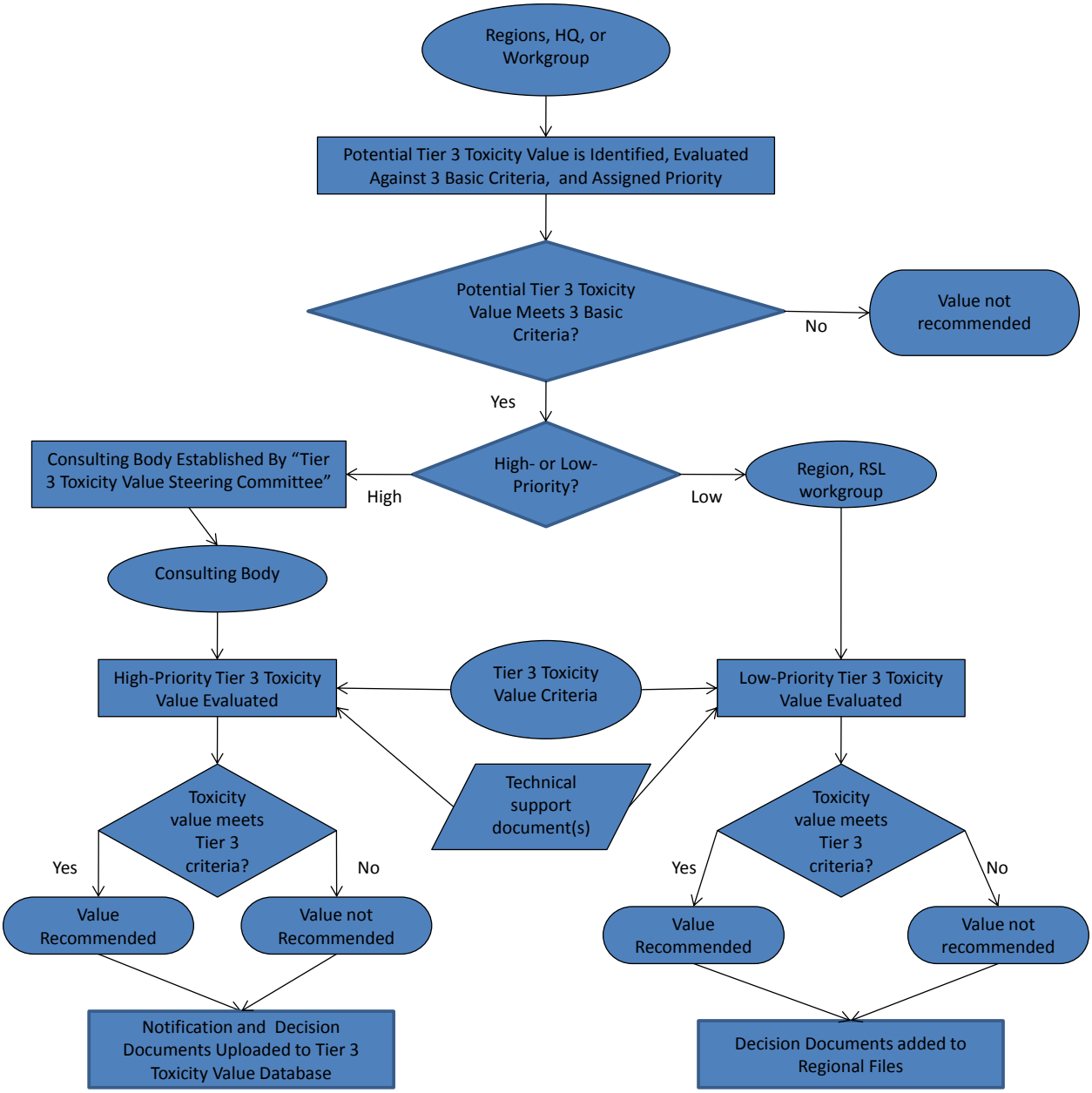
6 Recommended Option/Process and Path Forward

Overall, the Regional Tier 3 Toxicity Value Workgroup recommends a process that is flexible, consistent, efficient, and results in the evaluation and selection of Tier 3 toxicity values that are scientifically defensible. As discussed above, there is no "one size fits all," especially with respect to the decision-making body, for the evaluation and selection of Tier 3 toxicity values, and there are numerous combinations of potential processes for identifying, evaluating, selecting, and documenting Tier 3 toxicity values. Therefore, the following recommendations are provided as a path a candidate Tier 3 toxicity value may take from its initial identification to final selection and documentation. Figure 2 below illustrates this proposed path. Note that the recommendations apply to future Tier 3 toxicity values not already recommended by regional and headquarters risk assessors and the RSL table. However, those involved in the implementation of all or certain aspects of this white paper should consider existing Tier 3 toxicity values.

6.1 Toxicity Value Identification

The Tier 3 toxicity value workgroup recommends that the responsibility of identifying Tier 3 toxicity values remains with the regional and headquarters risk assessors and existing regional risk assessor workgroups (such as the RSL table team) to maintain flexibility and conserve time and resources. As discussed previously, these groups are most likely to encounter a potential Tier 3 toxicity value during development of a human health risk assessment and or a revision to the RSL table. Development of a formal workgroup, as discussed in Section 5.4.3.1, will require time and resources. Furthermore, as indicated in previous sections, the identification of potential Tier 3 values is not a frequent occurrence. Thus, the value of a formal workgroup is unclear, especially when regional risk assessors and others will likely continue to search for Tier 3 toxicity values in their routine work (risk assessments).

Figure 2. Proposed Tier 3 Toxicity Value Selection Process



6.2 Initial Evaluation and Chemical Prioritization

Beyond a more thorough and complete evaluation of a potential Tier 3 toxicity value, some steps must be taken to maintain a flexible and efficient process. We recommend that those who identify a potential Tier 3 toxicity value ensure that the toxicity value meets the three basic criteria outlined in Section 5.3.1, which include transparency, peer-reviewed, and public availability. Of course, these criteria are general in scope and a potential Tier 3 value meeting all three criteria at some level does not guarantee that it is scientifically defensible for use in human health risk assessments. At this time, other factors may also be considered and used to eliminate a potential Tier 3 value (for example, extrapolation of a toxicity value from an occupational standard, such as an Occupational Safety and Health Administration permissible exposure limit).

During the initial evaluation, this white paper recommends that the chemical be designated a low or high priority according to the prioritization criteria in Section 5.2. This designation is essential because it provides the basis for the recommendations in Section 6.3 on the type of consulting body to become involved. Note that additional prioritization of "high" priority chemicals will occur by the "Tier 3 Toxicity Value Steering Committee" (see Section 6.3.2.1). Because two of the prioritization criteria include the chemical's prevalence across the regions and level of interest at the national level (whether it would become the subject of a rule-making, for example), not to mention the potential subjective nature of those determinations, this white paper recommends that these efforts be coordinated with risk assessors and program representatives from other regions and headquarters via the "Tier 3 Toxicity Value Steering Committee."

6.3 Consulting Body

It is of the opinion of the Tier 3 toxicity value workgroup that no single process for evaluating and selecting a Tier 3 toxicity value will be the most efficient and timely for all potential scenarios where a potential Tier 3 toxicity value becomes available. Yet, the Tier 3 toxicity value workgroup also recognizes that a more formal process needs to be established to promote greater consistency and transparency among the regions. To meet these needs, this white paper recommends two separate approaches for evaluating and selecting a Tier 3 toxicity value. Because a chemical's significance and priority have previously defined the level of involvement by regional and headquarters risk assessors and toxicologists, it also serves as the critical determinant in selecting the appropriate approach. Specific details on the two approaches are provided in the following sections.

6.3.1 Low-Priority Chemicals

This white paper recommends that the Tier 3 toxicity values be evaluated and selected by the individual regions for chemicals that are designated as "low priority." However, this alternative does not necessarily preclude a region from consulting with others outside the region (such as STSC) regarding the use of a particular Tier 3 toxicity value. The "individual region" option appears to be the most practical for the "low-priority" chemicals, especially because it may allow for quicker decision making.

Chemicals with regional significance only, for example, may not draw enough interest from risk assessors from other regions or headquarters to staff workgroups, which could stall efforts to evaluate and select a value. A quick turnaround time is beneficial for non-risk driving chemicals so that it does not hold up decisions on risk-driving chemicals. Concerns with transparency and credibility are likely minimal for "low-priority" chemicals, especially non-risk driving chemicals. In addition, the RSL workgroup (under this approach) would continue to be responsible for evaluating and selecting Tier 3 toxicity values for "low-priority" chemicals because the RSL workgroup handles a wide array of chemicals ranging from "low priority" to "high priority."

6.3.2 High-Priority Chemicals

Even among high-priority chemicals, there may be varying expectations on the type of consult to be performed. Thus, it does not appear practical to recommend a specific consulting body. Instead, this white paper recommends a flexible and adaptive approach whereby potential Tier 3 toxicity value consultations be elevated to a "Tier 3 Toxicity Value Steering Committee." This committee (see Section 6.3.2.1) will be responsible for establishing the consulting body (such as an *ad hoc* workgroup, headquarters, or ADP) that best fits the situation and expectations of the risk assessors.

6.3.2.1 Tier 3 Toxicity Value Steering Committee

Although this white paper has not presented or evaluated potential workgroups that could fulfill the role as the "Tier 3 Toxicity Value Steering Committee," this white paper recommends that this role be subsumed by the OH2R2AF toxicity workgroup. This role falls within the scope of the OH2R2AF toxicity workgroup, which is to provide a forum to discuss and provide direction for OSWER human health risk assessors with regard to the use of toxicity values in removal and remedial actions. Furthermore, the OH2R2AF toxicity workgroup consists of members representing several regions and offices within headquarters. This broad range of representation enables the workgroup to more easily reach out to subject matter experts among the regions and headquarters, as well as to stay abreast of regional and national risk assessment issues that may affect the level of review that a potential Tier 3 toxicity value may receive.

Assuming the OH2R2AF toxicity workgroup takes on this responsibility, it may need to establish some guidelines or processes for elevating these chemicals and selecting the appropriate decision-making body. These guidelines and processes may include some of the following elements.

- Points of contact for elevating the chemical to the OH2R2AF toxicity workgroup.
- Criteria for determining which consulting entity will be used.
- Listing of subject matter experts (including regional and headquarters scientists and program representative) interested in participating in consultation workgroups.
- Who will be responsible for performing the review and evaluating the potential Tier 3 toxicity value's health risk assessment (will it be performed by the requestor, consultant, *ad hoc* workgroup members, or headquarters).

- Information requirements (health risk assessments and other documents pertaining to the derivation of a potential Tier 3 toxicity value).
- Who will be responsible for submitting consultation requests (for example, regional risk assessors, RTICs, managers, or division directors).

6.3.2.2 Other Considerations

This white paper generally recommends that the complete evaluation of potential high-priority Tier 3 toxicity values be the responsibility of the consulting body. This responsibility will ensure that subject matter experts are critically reviewing the underlying data behind a toxicity value. However, there is the potential that the consulting body may not perform the full review and evaluation. Previous examples include consultations on chromium VI and PCE. Consulting bodies may have time and resource constraints that prevent them (and individual members) from completing the full review and evaluation. In addition, duplication of effort may be of concern if the requestors perform this activity after a potential Tier 3 toxicity value has been initially identified as a matter of interest or routine. In these instances, consulting bodies may require that others (the requestor) perform the full review and evaluation of the toxicological support documentation and provide a summary of relevant information to the consulting body for additional evaluation and decision-making. The scope of the consulting body's review and evaluation of the underlying toxicological information may vary. As a result, decisions regarding the responsibility and extent of the review will likely require some degree of coordination with the original consultation requestor. These activities could be facilitated by a "Tier 3 Toxicity Value Steering Committee."

6.4 Toxicity Value Evaluation

Regardless of who is responsible for evaluating a potential Tier 3 toxicity value, the same set of criteria should be applied to all Tier 3 toxicity value evaluations. This white paper recommends that the ECOS criteria, guiding principles, and other relevant criteria and guidance outlined in the white paper be adopted as criteria for evaluating potential Tier 3 toxicity values. In addition to adopting the aforementioned criteria, this white paper also recommends that the confidence in the toxicity value be described in the evaluation. Evaluating and assigning confidence to toxicity values including the underlying study and overall database are standard practice and potentially critical elements in risk management decision-making. Confidence in a Tier 3 toxicity value would also be significant (a deciding factor) in instances where there are competing Tier 3 values.

Also, per Section 5.3.2, it is critical that those involved in the evaluation and selection process have, at a minimum, a basic understanding of how to evaluate and assess the data usability of toxicity studies, the adverse and critical effect levels in a study, and the methodologies used to derive toxicity values. Although these skills are likely to be present among the members of regional and headquarters workgroups, it is less certain at the "individual region" level. Thus, training and educational opportunities pertaining to the aforementioned skills should continue to be a priority among the risk assessors.

6.5 Documentation

The following recommendations on documentation are generally intended to address high-priority chemicals. In keeping with the theme of "low-priority" chemicals, decisions on how regions document and store "low-priority" Tier 3 toxicity values will be left to the regions and RSL workgroup. However, the Tier 3 toxicity value workgroup recommends that the regional risk assessors are notified of the selection of Tier 3 toxicity values in case these chemicals ever come up in other regions. To make this process efficient and less of a burden on the risk assessors who select a value, it is recommended that notification and storage of decision documents be coordinated through the "Tier 3 toxicity value steering committee."

6.5.1 Decision Documents

This white paper recommends that a formal system be put into place that documents selection of a Tier 3 toxicity value. This white paper further recommends that all decision documents for high-priority chemicals be provided in a formal memorandum from the selecting entity to the original requestor(s), "Tier 3 toxicity value steering committee" and other relevant workgroups, such as the RSL workgroup and the OH2R2AF toxicity workgroup (if different from the steering committee). The memorandum should provide the rationale for selecting a value (how it meets the evaluation criteria) and contain the following information (where applicable):

- Summary of underlying studies,
- Methods for toxicity value derivation,
- Uncertainty factors (RfDs and RfCs),
- Carcinogenic MOA and cancer classification (if available),
- Target organ/critical effect, and
- Confidence in toxicity value (critical for competing values).

The recommendation above also applies to situations where the consulting body does not recommend the use of a value or selects one value over another in the case of competing values. When a value is not selected, the response will focus on the particular criteria that are not met or other technical reasons for not recommending a value. If the rationale for rejecting a value is not documented, there is the potential that the same requests could be made in the future.

6.5.2 Repository

This white paper recommends that Tier 3 toxicity value decision documents and related documents (such as health risk assessments) be housed electronically at one of the existing EPA toxicity value websites or electronic libraries. To avoid duplication of effort, this white paper also recommends that

decision documents for toxicity values not selected by the consulting body be housed in the repository. Notwithstanding contractual and resource arrangements with EPA websites that contain toxicity value information, use of an existing EPA on-line location would not add to the number of EPA websites to search for a toxicity value and would make use of existing infrastructure and resources. In addition, it is recommended that the electronic library be publicly available and follow a format similar to the PPRTV electronic library (with drop-down menus)

Those involved in posting Tier 3 toxicity value consults, such as the "Tier 3 toxicity value steering committee," will have to consider whether the health risk assessment in support of a particular toxicity value needs to be posted on the website and if so, how this information will be housed. Health risk assessments can be lengthy documents, and posting them on EPA websites may not be feasible. However, health risk assessments in support of toxicity values are often provided electronically by the authors, which are typically federal and state health agencies (as is the case with ATSDR toxicological profiles). Therefore, links to websites containing those assessments may suffice.

7 Summary

While EPA has multiple policies, guidance, and guidelines to assist and/or direct risk assessors in the development and selection of toxicity values, specific guidance on selecting tier 3 toxicity values for use in Superfund and RCRA cleanup programs is limited. As a result, regional risk assessors have shared concerns over transparency and consistency of selecting Tier 3 toxicity values. In response, the Tier 3

Toxicity Workgroup developed this white paper to explore and recommend processes for enhancing the selection of Tier 3 toxicity values.

The process of selecting Tier 3 toxicity values consists of several steps including the identification, prioritization, evaluation, selection, documentation, and communication of Tier 3 toxicity values. Chapters 1 and 2 provide background on guidance and policies regional risk assessors follow to identify toxicity values and examples of some of the most commonly used federal, state and international sources of Tier 3 toxicity values and toxicity data. Chapter 2 also introduced the similarities and differences in how toxicity values are developed within each of those sources and recommended that a basic understanding on how to evaluate and assess the data usability of toxicity studies, identify the adverse and critical effect levels in a study and evaluate the regulatory-specific methodologies used to derive toxicity values is useful for comparing, selecting, and developing chemical-specific toxicity values. A number of publications, both internal and external to EPA, are summarized in Chapter 3, which provide guidance on how to evaluate the underlying basis of a toxicity value and provide a suggested framework for identifying and selecting toxicity values. Chapter 4 summarizes current and past practices of how regional risk assessors have identified, evaluated, and selected Tier 3 toxicity values.

Chapter 5 explores various options for identifying, evaluating, selecting, and documenting Tier 3 toxicity values. The chapter discusses alternatives for who would be responsible for identifying potential Tier 3 toxicity values and proposes a set of criteria for assigning priority to a chemical because a chemical's priority will likely dictate the entity that will provide a Tier 3 consultation. Chapter 5 also proposes a process for evaluating and selecting Tier 3 toxicity values, which includes two steps consisting of a basic evaluation and a critical review. The remainder and bulk of the chapter explores the options for Tier 3 toxicity value consultations and options for documenting and communicating the evaluation and selection of Tier 3 toxicity values. The options for documenting and communicating the selection of Tier 3 toxicity values include methods on how to document and distribute decision documents to regional risk assessors and alternatives for warehousing decision documents. The options for the Tier 3 toxicity value consultation process are summarized in the table below.

After consideration of the strengths and limitations of each of the alternatives and previous and current methods of selecting Tier 3 toxicity values, this white paper recommends a general process that retains flexibility, but also enhances consistency and transparency. Rather than recommend a “one size fits all” approach that could hinder efficiency and lengthen decision-making, this white paper recommends two approaches, one addressing low priority chemicals and the other addressing high priority chemicals. Proposed criteria for assigning priority are presented in Section 5.2.

For low priority chemicals, this white paper recommends that Tier 3 toxicity value decision-making be retained within the regions. While responsibility for selecting Tier 3 toxicity values remains within the regions, this white paper encourages regions to consult others outside of their own region, such as the OH2R2AF, RSL workgroup, and STSC. Regions may lack information, resources, and technical expertise to conduct chemical prioritizations and to evaluate and select Tier 3 toxicity values.

In regard to high priority chemicals, this white paper recommends the establishment of a "Tier 3 Toxicity Value Committee" that will be responsible for the overall coordination of the Tier 3 toxicity value selection process. The "Tier 3 Toxicity Value Committee," a role that can be subsumed by the OH2R2AF toxicity workgroup, would be mainly responsible for establishing the consulting body, i.e., the group responsible for evaluating and selecting a Tier 3 toxicity value, that best fits the needs and expectations of the risk assessors for the specific chemical. In addition, while decisions on how regions document and store "low priority" Tier 3 toxicity values will be left to the regions and RSL workgroup, a more formal and structured process for documenting, storing, and communicating "high priority" Tier 3 toxicity value selections is recommended. Specifically, this white paper recommends that all decision documents be provided in a formal memo from the reviewers to the requestor and would apply to situations where a toxicity value is recommended, not recommended, or one value is recommended over another, i.e., competing toxicity values. Furthermore, this whitepaper recommends that decisions be communicated to the regional risk assessors, via the "Tier 3 Toxicity Value Committee," and that the decision documents and other relevant information (e.g., health risk assessments) be stored within existing EPA toxicity value websites or electronic libraries.

Although this white paper recommends two approaches, it is important to point out that they both share some common recommendations including elements of the identification, prioritization, and evaluation steps. These common recommendations include, but are not limited to, prioritization criteria (discussed above) and the criteria and guiding principles used to evaluate candidate Tier 3 toxicity values. Regardless of the vehicle used to perform the evaluations, the same set of criteria and principles should be used to evaluate all potential Tier 3 toxicity values. Furthermore, to ensure consistent and proper application of review criteria, training will continue to be a critical for those individuals that may be involved in the evaluation and selection process.

Table 1. Options for Tier 3 Consultations

Option	Factors for Consultation	Strengths	Limitations
Action Development Process (ADP) Workgroup	ADP is the Agency's method for producing high quality actions such as regulations, policies, and risk assessments. Tier 3 toxicity values considered influential scientific information should be developed through ADP. Process typically initiated by Office of Solid Waste and Emergency Response (OSWER). Tiering process begun by Regulatory Steering Committee based on level of senior management involvement and extent of cross-agency influence: • Tier 1—actions signed by Administrator and have broad cross-agency influence • Tier 2 – actions signed by assistant Administrator and have some cross-agency influence • Tier 3 – actions signed by Office directors and have limited cross-agency influence	**	**
Headquarters Consultation	Regions submit requests to Headquarters. Typically, consultations are led by OSWER with input from the Office of Research and Development (ORD). Consultations are often coordinated among offices of OSWER including the Science Advisor, OSTRI, and OEM. Currently primarily performed on an "informal" basis. Could be formalized in future with consistent designated lead office within OSWER. Key factors include: • Headquarters establish contact to receive Tier 3 requests • Regional risk assessors establish a consistent process for submitting requests • Contract support may be necessary to assist within consultation	• Promote consistency among regions • More likely to maintain consistent process for providing consultations • Add "greater weight and credibility to Tier 3 values	• Perception that Headquarters is setting policy • Not well-suited to handle low-priority chemicals
Regional Workgroup	Formal or ad hoc group of subject matter experts with expertise relevant to chemicals being evaluated. Led and generally consisting of regional risk assessors and toxicologists. Primary focus would be on low- to medium-priority chemicals. Two existing regional workgroups: • Regional screening level (RSL) workgroup • Regional human health risk assessment forum (OH2R2AF) toxicity workgroup	Formal workgroup • Easier establishment and tracking of expectations and results • Visible to headquarters and regions resulting in greater credibility of Tier 3 values • Maintenance of consistent process Ad hoc workgroup • Formed with selected experts as necessary • May better champion needs and priority for regional-specific Tier 3 values • If well coordinated, will maximize results by spreading duties to many, rather than few	Formal workgroup • Fixed membership may fail to reach out to individuals/groups with particular expertise • Workload may not require regular meetings, resulting in loss of focus and interests among members Ad hoc workgroup • May lack effectiveness if not well-coordinated • Formation and staffing of multiple ad hoc workgroups may be cumbersome • May suffer from lack of headquarters input • Reduced likelihood of consistent process
Joint Headquarters/Regional Workgroup	Joint workgroup consisting of regional and headquarters risk assessors and toxicologists Similar to regional workgroup except the group could be led by either headquarters or regional individual and have members from both groups.	Similar to regional workgroup, as well as • Allows more coordination between headquarters and regions resulting in greater transparency and credibility of Tier 3 values • More likely to include subject matter experts from headquarters (as compared to regional workgroup)	Similar to regional workgroup, as well as • Sharing of power between headquarters and regions could limit effectiveness • Competing interests could slow workgroup activity
Individual regions	Individual regions would continue to use current methods for identifying and selecting Tier 3 values. Anticipated for use primarily with low- to medium-priority chemicals; high priority chemicals expected to include headquarters input.	• Relatively quick turn-around • Allows regions to maintain control of Tier 3 values • Allows development of more complete and thorough risk assessment	• Potential lack of transparency and reduced credibility of Tier 3 values • Lack of cross-regional approach limits access to and use of varied regional expertise • Approach does not address high priority chemicals which require headquarters input • Potential lack of regional resources and expertise in evaluating and selecting a Tier 3 value

** Unlike the other options, the ADP generally applies to specific circumstance as indicated in Section 5.4.1, i.e., Tier 3 toxicity values that are considered highly influential scientific information. Thus, the strengths and limitations of the ADP were not evaluated in this white paper.

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Appendix A – OSWER and ORD Organizational Charts

Figure A-1. Office of Solid Waste and Emergency Response

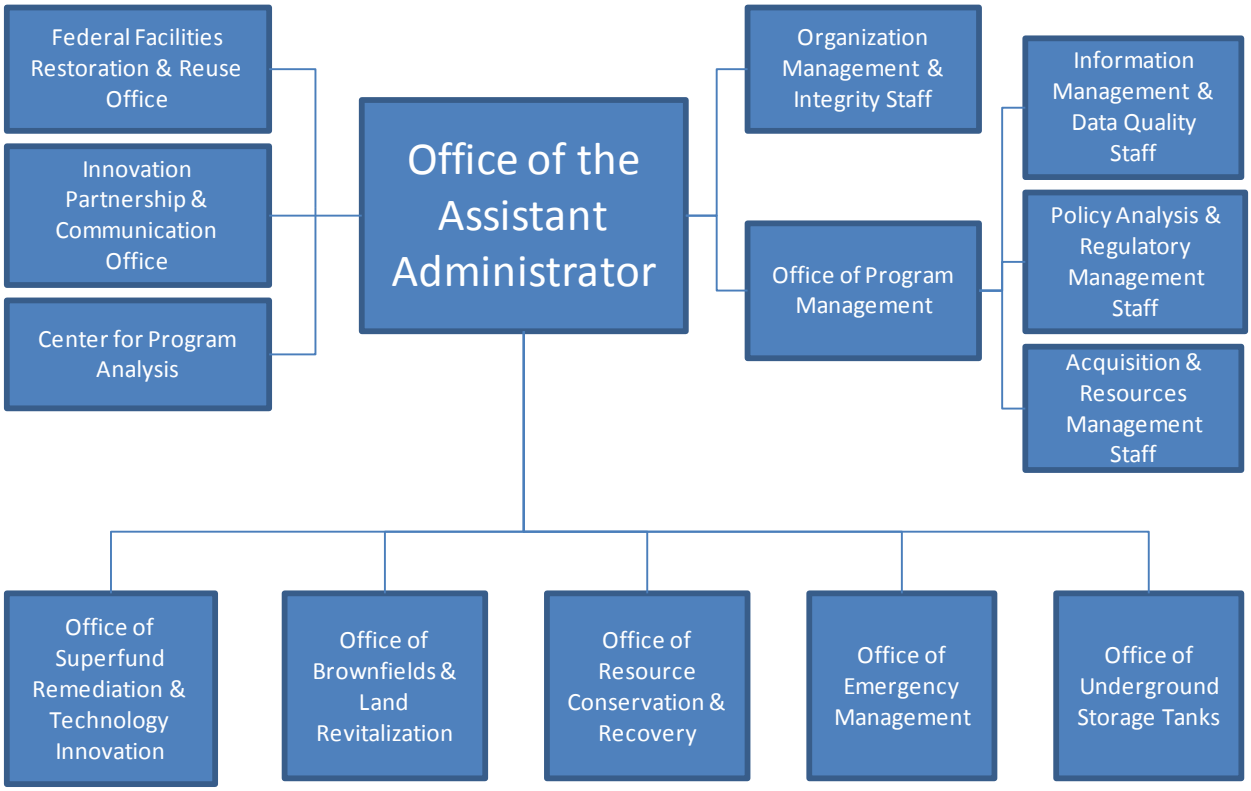
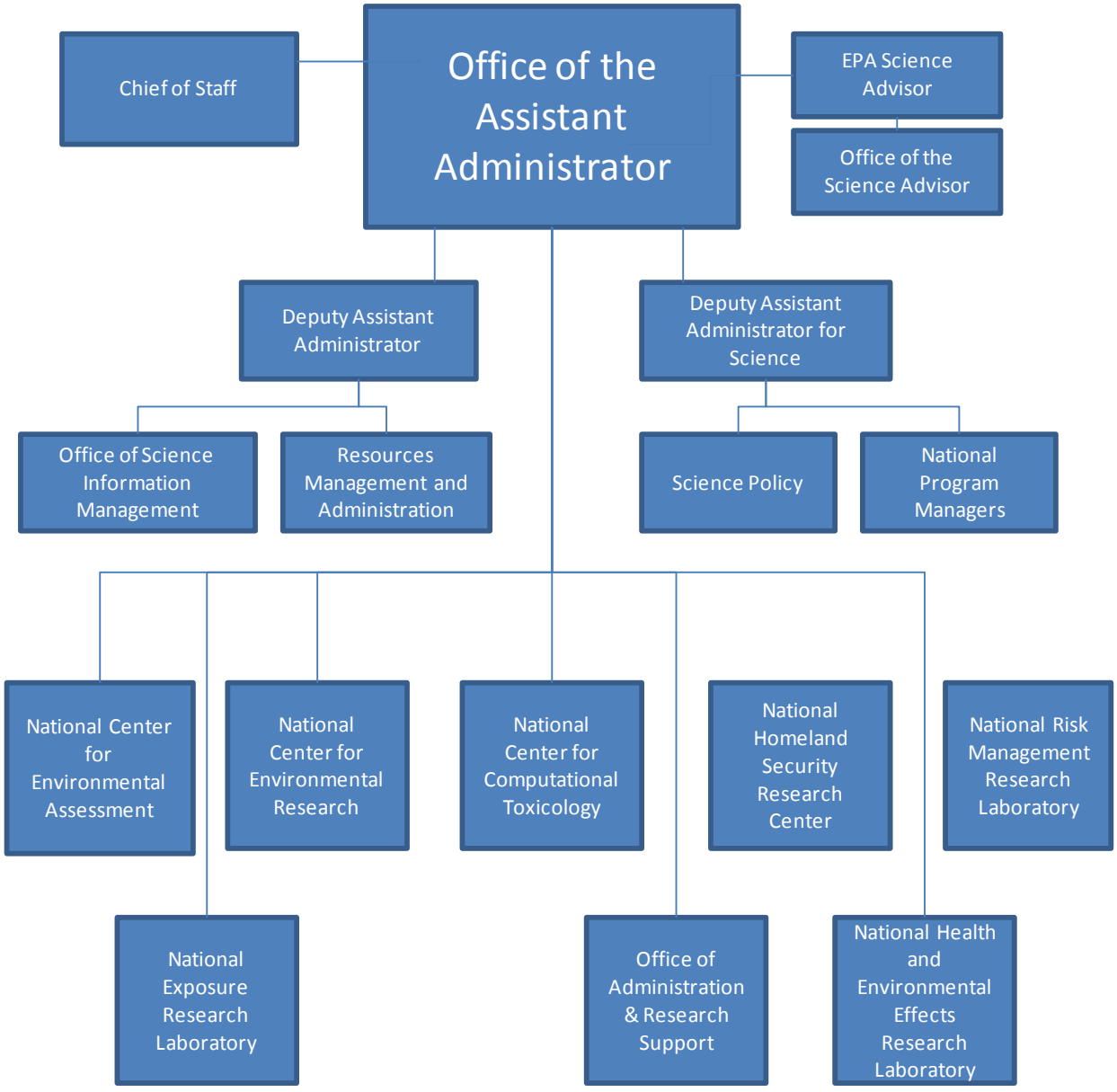


Figure A-2. Office of Research and Development



Appendix B – Consultations

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APR - 9 2009

OFFICE OF
SOLID WASTE AND EMERGENCY
RESPONSE

MEMORANDUM

SUBJECT: Withdrawal of the January 15, 2009, OSWER Guidance Entitled "Interim Recommended Trichloroethylene (TCE) Toxicity Values to Assess Human Health Risk and Recommendations for the Vapor Intrusion Pathway Analysis"

FROM: Barry N. Breen, Acting Assistant Administrator
Office of Solid Waste and Emergency Response

TO: Acting Regional Administrators, Regions 1 - 10

On January 15, 2009, the Office of Solid Waste and Emergency Response (OSWER) issued a guidance memorandum entitled "Interim Recommended Trichloroethylene (TCE) Toxicity Values to Assess Human Health Risk and Recommendations for the Vapor Intrusion Pathway Analysis." That guidance was subsequently distributed to EPA regional staff and managers. The Agency is withdrawing this guidance to further evaluate the recommendations regarding the non-cancer TCE toxicity value for use in risk assessments of inhalation exposures. Once this re-evaluation is complete, we will update you.

In the interim, toxicity values for TCE should be determined consistent with the National Contingency Plan (e.g., 40 CFR 300.430(e)) and the 2003 Toxicity Hierarchy (OSWER Directive 9285.7-53, December 5, 2003). The Directive provides guidance on a hierarchy of approaches regarding human health toxicity values in risk assessments, and provides guidance for regional risk assessors to help them identify appropriate sources of toxicological information that should generally be used in performing human health risk assessments at Comprehensive Environmental Response, Compensation and Liability Act (CERCLA or "Superfund") sites. This hierarchy of approaches is also appropriate for human health risk assessments at Resource Conservation and Recovery Act (RCRA) corrective action sites.

The guidance memorandum also addressed the vapor intrusion pathway and recommended a multiple lines of evidence approach in assessing sites for vapor intrusion. EPA expects to issue a separate document that will address the multiple lines of evidence approach as it relates to the vapor intrusion pathway.

If you have any questions, please contact Jayne Michaud in the Office of Superfund Remediation and Technology Innovation at 703-603-8847 or Mary Cooke in the Federal Facilities Restoration and Reuse Office at 703-603-8712.

cc: Regional Superfund Division Directors
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

REGION 7
901 NORTH 5TH STREET
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APR 2 9 2009

MEMORANDUM

SUBJECT: Recommended Risk-Based Human Health Screening Levels and Interim Trichloroethylene Toxicity Values Update

FROM: Jeffery Robichaud
Chief
ENSV/EAMB

TO: AWMD – RCRA Branch Chiefs
SUPR – All Division Branch Chiefs

The purpose of this memo is to update the Region 7 RCRA and Superfund programs on the recommended risk-based human health screening levels and to provide recommendations on trichloroethylene (TCE) chronic toxicity values. As a reminder, the recommendations provided in this memo apply to risk assessment-related documents developed by or on behalf of EPA Region 7, as well as any relevant documents submitted to the Region for review and approval.

In a memo, dated December 14, 2007, the Region 7 risk assessors recommended the use of the Region 6 Human Health Medium-Specific Screening Levels (MSSLs) as the primary source of screening levels. At that time, the Region 6 MSSLs were recommended because they were regularly updated and were consistent with current toxicity values and EPA risk assessment guidance and policy. Also, as indicated in that memo, a regional effort was underway to consolidate the existing regional screening tables into a single set of screening values in order to improve consistency and incorporate updated guidance. In the fall of 2008, that effort was completed and the Regional Screening Table was posted on the Region 3 website, followed later by Regions 9 and 6.

Given that the Regional Screening Table is now available on the internet, the Regional risk assessors recommend the use of the Regional Screening Table and its supporting documents (e.g., User's Guide). The links to the table and supporting documentation are provided below.

- Region 3, http://www.epa.gov/reg3hwmd/risk/human/index.htm.
- Region 6, http://www.epa.gov/Region6/6pd/rcra_c/pd-n/screen.htm.
- Region 9, http://www.epa.gov/region09/superfund/prg/index.html.

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Also, we have provided additional information to consider when using the tables. That information is provided below.

- Although Regions 3, 6, and 9 continue to use the Risk-Based Concentration (RBC), Preliminary Remediation Goal (PRG), and Medium-Specific Screening Level (MSSL) terminology on their respective websites, they all provide the same Regional Screening Table and supporting documents. Risk assessments and related documents should cite the Regional Screening Table.
- The inhalation exposure pathway screening level equations are consistent with EPA's inhalation dosimetry methodology (USEPA, 1994). Inhalation unit risk (IUR) and reference concentration (RfC) toxicity values are used in place of inhalation cancer slope factors and inhalation reference doses, respectively. Therefore, body weight and inhalation rate are no longer used when evaluating the inhalation pathway. This slightly impacts all screening levels and risk estimates that are based solely, or in part, on the inhalation exposure pathway.
- The Regional Screening Table provides a screening level for industrial air.
- The dermal contact pathway is not accounted for in the tap water screening levels.

With regards to TCE, it is currently undergoing reassessment by the Integrated Risk Information System (IRIS) program and interagency review and external peer review of the draft assessment are projected to begin in the fourth quarter of fiscal year (FY) 2009 and first quarter FY 2010, respectively. Until IRIS provides final toxicity values, specific guidance is provided by EPA headquarters, or new toxicity values become available that fall within EPA's toxicity value hierarchy (e.g., PPRTV database), we recommend the use of the following chronic toxicity values for TCE. When evaluating cancer risks, we recommend the use of California Environmental Protection Agency's (CalEPA) oral slope factor (SFo) of 0.013 $(mg/kg\text{-}day)^{-1}$ and IUR of 2.0E-06 $(\mu g/m^3)^{-1}$. When evaluating chronic non-cancer health hazards, we recommend the use of New York State Department of Health's (NYSDOH) air criterion of 10 $\mu g/m^3$. An oral reference dose (RfDo) is not available at this time and until one becomes available, we recommend that the uncertainties regarding the lack of the value be discussed in site-specific human health risk assessments. The use of these toxicity values is consistent with OSWER Directive 9285.7-53, which is OSWER's current policy on the selection of toxicity values in human health risk assessments. All three values have undergone peer review and are Tier 3 toxicity values.

Also, please note that CalEPA provides a chronic inhalation non-cancer toxicity value for TCE which is 60-fold greater than NYSDOH's air criterion. However, it is our professional judgment that CalEPA's Recommended Exposure Limit (REL) does not afford an adequate level of protection for long-term exposures to TCE and therefore, it should not be used in Superfund or RCRA Corrective Action risk assessments (and related documents) submitted to or conducted on behalf of EPA Region 7. Our reasons for supporting the use of the NYSDOH's non-cancer air criterion include, but are not limited to, the following:

- The NYSDOH value is based on more extensive presentation of health endpoints.
- The NYSDOH value is based on a more recent evaluation of the available health effects

literature, such as developmental and reproductive effects.

- The NYSDOH's critical study has clear strengths over CalEPA's REL critical study. First, the Rasmussen et al. (1993) study, which was used to derive NYSDOH's air criterion, had 99 subjects compared to CalEPA's critical study, the Vandervort and Polankoff (1973) study, which included 19 subjects. Second, the Rasmussen study evaluated clinical neurological endpoints whereas the Vandervort and Polankoff study looked at self-reported health endpoints via a questionnaire. Also, the Rasmussen study included concurrent biological monitoring that was used to estimate TCE air concentrations via pharmacokinetic modeling. The Vandervort and Polankoff study derived an exposure concentration from one day measurements.
- The lowest-observed-adverse-effect-level (LOAEL) used to derive the NYSDOH air criterion is $1/6^{th}$ the LOAEL used to derive the CalEPA REL.
- CalEPA's chronic REL is greater than the Agency for Toxic Substances and Disease Registry's (ATSDR) intermediate Minimal Risk Level (MRL), which covers exposures lasting from 14 days to 1 year. Although the ATSDR intermediate inhalation MRL is based on the subchronic rat study by Arito et al. (1994), the human pharmacokinetic adjusted LOAEL is similar to that of the human equivalent LOAELs observed in several human studies including the studies used by CalEPA and NYSDOH to derive chronic non-cancer inhalation values (NRC, 2006). Note that the ATSDR intermediate MRL is a peer-reviewed value that is recommended for use when evaluating subchronic exposures.

If you or your staff have any questions or need assistance regarding the Regional Screening Table or TCE's toxicity values, please contact Mike Beringer at x7351, Jeremy Johnson at x7510, Greg McCabe at x7709, or Kelly Schumacher at x7963. Specific questions on TCE's reassessment should be direct to Jeremy Johnson, the Region 7 IRIS Consensus Reviewer.

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Attachment

U.S. ENVIRONMENTAL PROTECTION AGENCY, REGION II
Emergency and Remedial Response Division
290 Broadway
New York, New York 10007-1866

MEMORANDUM

TO: William Sette, Senior Science Advisor, Office of Solid Waste and Emergency Response

FROM: Chloe Metz, Risk Assessor, Emergency and Remedial Response Division, Region 2

DATE: August 17, 2009

RE: Classification of the Oral Slope Factor for Hexavalent Chromium (Cr VI) Developed by New Jersey as a Tier 3 Toxicity Value

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As defined in OSWER directive 9285.7-53, a Tier 3 value, "Includes additional EPA and non-EPA sources of toxicity information. Priority should be given to those sources of information that are the most current, the basis for which is transparent and publicly available, and which have been peer reviewed." Region 2 believes that the oral slope factor for Cr VI of 0.5 $(mg/kg\text{-}day)^{-1}$ developed by Alan Stern of the New Jersey Department of Environmental Protection meets the above definition. The assessment is current (released in July, 2009) and was subject to an external peer review which is available online (http://www.state.nj.us/dep/dsr/chromium/peer-review-comments.pdf). Added support for the use of this OSF as a Tier 3 value is the fact that EPA-NCEA reviewed the draft risk assessment and concluded that it was, "Clearly written, understandable, and well organized, and it was, for the most part, consistent with EPA's risk assessment methodologies."

The hierarchy directive goes on to say that, "Consultation with the STSC or headquarters program office is recommended regarding the use of the Tier 3 values for Superfund response decisions when the contaminant appears to be a risk driver for the site." As such, Region 2 respectfully requests that OSWER provide written support for the use of the New Jersey OSF for Cr VI to determine action levels for the Garfield site where Cr VI is the only contaminant of concern.

References

New Jersey Department of Environmental Protection (April, 2009). Derivation of Ingestion-Based Soil Remediation Criterion for Cr^{+6} Based on the NTP Chronic Bioassay Data for Sodium Dichromate Dihydrate. http://www.state.nj.us/dep/dsr/chromium/soil-cleanup-derivation.pdf

United States Environmental Protection Agency, Office of Solid Waste and Emergency Response (2003). Human Health Toxicity Value in Superfund Risk Assessments. Directive No. 9285.7-53. http://www.epa.gov/oswer/riskassessment/pdf/hhmemo.pdf

cc: Michael Sivak
Helen Dawson
Stiven Foster
Janine Dinan
Dave Crawford

Re: Classification of the Oral Slope Factor for Hexavalent Chromium (Cr VI) Developed by New Jersey as a Tier 3 Toxicity Value

William Sette to: Chloe Metz 09/28/2009 02:39 PM

Cc: Dave Crawford, Helen Dawson, Janine Dinan, Michael Sivak, Stiven Foster, Barbara Hostage

History: This message has been replied to and forwarded.

TO: Chloe Metz, Risk Assessor, Emergency and Remedial Response Division, Region 2

FROM: William F. Sette, Senior Science Advisor, Office of Solid Waste and Emergency Response (5103T)

RE: Classification of the Oral Slope Factor for Hexavalent Chromium (Cr VI) developed by New Jersey as a Tier 3 Toxicity Value

The purpose of this email is to provide written confirmation of OSWER's concurrence with Region 2 using the oral cancer slope factor for Cr VI recently finalized by the state of New Jersey. As noted in your memo, attached below, this toxicity value is based on the most recent science, has been peer reviewed, is publicly available, and, in the opinion of EPA's ORD, is "clearly written, understandable,and well organized", i.e. transparent. Thus, it fulfills all of OSWER's criteria for a Tier 3 Toxicity Value. Janine Dinan of the Office of Emergency Management, which is the lead OSWER office for this emergency cleanup activity, as well as Dave Crawford, in the Office of Superfund Remediation and Technology Innovation, and I, concur with this conclusion. If you have any further questions, please feel free to contact me.

William F. Sette, Ph.D.
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202 566 1928
202 566 1934 fax
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Chloe Metz Bill, Attached is the memo we discussed. Plea... 08/17/2009 05:43:02 PM

From: Chloe Metz/R2/USEPA/US
To: William Sette/DC/USEPA/US@EPA
Cc: Stiven Foster/DC/USEPA/US@EPA, Michael Sivak/R2/USEPA/US@EPA, Janine Dinan/DC/USEPA/US@EPA, Helen Dawson/DC/USEPA/US@EPA, Dave Crawford/DC/USEPA/US@EPA
Date: 08/17/2009 05:43 PM
Subject: Classification of the Oral Slope Factor for Hexavalent Chromium (Cr VI) Developed by New Jersey as a Tier 3 Toxicity Value

Bill,

Attached is the memo we discussed. Please let me know if you have any questions. Thanks very much for your assistance throughout this process.

Best,

Chloe

Cr VI Tier 3 Memo.doc

Chloe Metz
Special Assistant
Emergency and Remedial Response Division
US EPA, Region 2
290 Broadway, 19th Floor
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212.637.3955 (voice)
212.637.4439 (fax)

Cr+6 Muta MOA for Carcinongenicity paper is published

William Sette to: Chloe Metz, Dave Crawford, Helen Dawson, Janine Dinan, Michael Sivak, Stiven Foster, Barbara Hostage 09/29/2009 10:02 AM

Cc: Michael Beringer, Nancy McCarroll

History: This message has been replied to and forwarded.

hi;

Attached please find this paper reflecting OPP's analysis that finds that this chemical has a mutagenic mode of action for carcinogenicity and that recommends that ADAFs be applied, consistent with EPA's Cancer Guidelines.

So it's recent, publically available, peer reviewed, and I leave the transparent open until we read it. That's all the criteria for Tier 3 use.

Bill

[attachment "McCarroll et al 2009.pdf" deleted by Chloe Metz/R2/USEPA/US]

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
SOLID WASTE AND EMERGENCY
RESPONSE

June 12, 2003

OSWER No. 9285.7-75

Marcia L. Bailey, D. Env.
Environmental Toxicologist
U.S. Environmental Protection Agency, Region 10
Office of Environmental Assessment, Risk Evaluation Unit
1200 Sixth Avenue, OEA-095
Seattle, Washington 98101

Dear Dr. Bailey:

I am responding to recent inquiries concerning cancer toxicity values to evaluate inhalation and ingestion risks from exposure to tetrachloroethylene, also commonly known as perchloroethylene or "PCE," and specifically whether it would be appropriate to use a California Environmental Protection Agency (Cal EPA) inhalation unit risk value and oral slope factor. This letter supercedes an earlier version of this letter, which identified an incorrect source of the oral slope factor. This letter is consistent with the earlier letter regarding the inhalation unit risk value and its source.

In the absence of relevant values in the U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS) or a value from EPA's National Center for Environmental Assessment/Superfund Technical Health Risk Support Center (STSC), which are the first two tiers of human health toxicity values in the EPA Superfund hierarchy, we would support consideration of the Cal EPA inhalation unit risk value from the Air Toxics Hot Spots Program and the oral slope factor from the Cal EPA Public Health Goal in Drinking Water.

In general, Cal EPA develops its toxicity values in a manner which is quite similar to the EPA IRIS program, in that many of the same databases and considerations are used. Cal EPA's assessments used information from some of the same sources or studies that EPA typically considers in the IRIS program, including the most recent relevant studies known to exist, and also considered this information in a manner similar to the EPA IRIS program.

In summary, having consulted on this matter with the STSC, the Office of Emergency and Remedial Response (OERR) supports use of the Cal EPA Air Toxics Hot Spots Program inhalation unit risk of 5.9 E-6 $(\mu g/m^3)^{-1}$ for Superfund sites as the best value available at this time until a U.S. EPA value becomes available. Having consulted with the STSC about the Cal EPA Public Health Goal in Drinking Water oral slope factor of 5.4E-1 $(mg/kg\text{-}day)^{-1}$ for PCE, we also support the use of this value until a U.S. EPA value becomes available.

The Cal EPA presents a full, complete and transparent presentation of the relevant information on their development of these values on their internet website. Documentation on the Air Toxics Hot Spots Program inhalation unit risk value can be found at this internet website: http://www.oehha.ca.gov/air/hot_spots/pdf/TSDNov2002.pdf . Since this website does not take you directly to the PCE discussion, and this can be difficult to find on the internet website, we have downloaded the eight pages pertaining to PCE and include them as an enclosure to this letter. Documentation on the Public Health Goal in Drinking Water oral slope factor can be found at this Cal EPA internet website: http://www.oehha.ca.gov/water/phg/pdf/PCEAug2001.pdf Because of the size of this document (75 pages) and because this website does take you directly to this document, we have not included this document as an enclosure to this letter. With respect to the transparency of any Superfund Program decisions which may use these values in selecting a response action, we recommend that the appropriate documentation from the Cal EPA website be provided, or the link to the relevant Cal EPA internet website be identified.

Thank you for your inquiry. If you have any questions, please contact Mr. Dave Crawford of my staff at (703) 603-8891.

Sincerely,

/s/

Elizabeth Southerland, Deputy Director
Office of Emergency and Remedial Response

cc: Harlal Choudhury ORD/NCEA/STSC
Sarah Levinson, Region 1
Matthew Hale, OSWER/OSW
Barnes Johnson, OSWER/OSW
Renee Wynn, OSWER/FFRO
James Woolford, OSWER/FFRO
Regional Risk Leads, Regions 1-10
Nancy Riveland, Superfund Lead Region Coordinator, USEPA Region 9
Paul Sieminski, RCRA Lead Region Coordinator, USEPA Region 6
OERR NARPM Co-Chairs
Joanna Gibson, OERR Document Coordinator

Enclosure: California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Air Toxics Hot Spots Program Risk Assessment Guidelines, Part II, Technical Support Document for Describing Available Cancer Potency Factors, December 2002 (excerpt pertaining to tetrachloroethylene)

PERCHLOROETHYLENE

CAS No: 127-18-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1998)

Molecular weight	165.83
Boiling point	121°C
Melting point	-19 °C
Vapor pressure	18.47 mm Hg @ 25°C
Air concentration conversion	1 ppm = 6.78 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 5.9 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 2.1 E-2 $(mg/kg\text{-}day)^{-1}$
[Male mouse hepatocellular adenoma and carcinoma incidence data (NTP, 1986), cancer risk estimate calculated using a linearized multistage procedure and PBPK model dose adjustment (CDHS, 1991).

III. CARCINOGENIC EFFECTS

Human Studies

Epidemiological studies of perchloroethylene (PCE) exposure have been reviewed by Reichert (1983) and by the U.S. EPA (1985). Blair *et al.* (1979) analyzed the death certificates of 330 union laundry and dry-cleaning workers (out of a cohort of 10,000). Of 330 decedents, 279 had worked solely in dry-cleaning establishments. Increased mortality from cancers of the respiratory tract, cervix, and skin was documented, and when all malignancies were evaluated together, the number of observed deaths was significantly greater than expected ($p < 0.05$). Although an excess of liver cancer and leukemia was also observed, these increases were not statistically significant.

In an expanded study, Blair *et al.* (1990) reported on mortality among 5,365 dry cleaning union members. Statistically significant excesses of cancer of the esophagus and cervix and non-significant excesses for cancer of the larynx, lung, bladder, and thyroid were reported. Lack of PCE exposure data and lack of accounting for potential confounding factors, such as economic status, tobacco, or alcohol use, prevents any firm conclusion as to the association of PCE exposure and excess cancer.

Katz and Jowett (1981) analyzed the mortality patterns of 671 white female laundry and dry-cleaning workers. Occupational codes listed on the certificates did not distinguish between the two types of work. Data on the duration of employment were not available, nor were the investigators able to determine to which solvent(s) the individuals were exposed. Smoking history was not known. A significant increase in risk of death from cancer of the kidneys ($p < 0.05$) and genitals ($p < 0.01$) was

documented. An excess risk from skin and bladder cancer was also found; however, neither increase was statistically significant.

Other studies of laundry and dry-cleaning workers have also reported an increased risk of death from cervical cancer (Blair *et al.,* 1979; Kaplan, 1980); however, these investigators have not compared mortality data by low-wage occupation. Although not definitive, the findings of Katz and Jowett (1981) suggest that factor(s) other than (or in addition to) solvent exposure are important contributors to cervical cancer.

Kaplan (1980) completed a retrospective mortality study of 1,597 dry-cleaning workers exposed to PCE for at least one year (prior to 1960). The solvent history of approximately half of the dry-cleaning establishments was known. The inability of Kaplan to quantify solvent exposure adds an important confounding variable to the study (Kaplan, 1980). The mean exposure concentration of individuals to PCE was calculated to be 22 ppm for dry-cleaning machine operators and 3.3 ppm for all other jobs. Kaplan found an elevated SMR (182) for malignant neoplasms of the colon (11 observed deaths, 6.77 to 6.98 expected deaths). In addition to colon cancer, malignant neoplasms of the rectum, pancreas, respiratory system, urinary organs, and "other and unspecified sites (major)" were observed (Kaplan, 1980). Although the relatively small cohort in this study limits conclusions about the carcinogenic potential of PCE, the study (Kaplan, 1980) results suggest a relationship between colon cancer and solvent exposure.

A group of Danish laundry and dry-cleaning workers was identified from the Danish Occupational Cancer Register (Lynge *et al.,* 1990). From cancer incidence data for a 10-year period, a significant excess risk was found for primary liver cancer among 8,567 women (standardized incidence ratio 3.4, 95% confidence interval 1.4-7.0). No case of primary liver cancer was observed among 2,033 men, for whom the expected value was 1.1. Excess alcohol consumption did not appear to account for the excess primary liver cancer risk for women. However, no data was available on actual exposures of the study group to PCE or other chemicals.

Duh and Asal (1984) studied the cause(s) of mortality among 440 laundry and dry-cleaning workers from Oklahoma who died during 1975 to 1981. Smoking histories were not available and separation of the two groups by occupation was not possible. NIOSH reported that, although 75% of dry-cleaning establishments in the U.S. use PCE, Oklahoma may be unique in that petroleum solvents account for more that 50% of total solvents used during this period (NIOSH, 1980). Analysis of deaths due to cancer showed an increase for cancers of the respiratory system, lung, and kidney.

Brown and Kaplan (1987) conducted a retrospective, cohort-mortality study of workers employed in the dry-cleaning industry to evaluate the carcinogenic potential from occupational exposure to PCE. The study cohort consisted of 1,690 members of four labor unions (located in Oakland, Detroit, Chicago, and New York City). Individuals selected for the study had been employed for at least one year prior to 1960 in dry-cleaning shops using PCE as the primary solvent. Complete solvent-use histories were not known for about half of the shops included in the study. Because petroleum solvents were widely used by dry cleaners prior to 1960, most of the cohort had known or potential exposure to

solvents other than PCE (primary, various types of Stoddard solvents). The investigators also identified a subcohort of 615 workers who had been employed only in establishments where PCE was the primary solvent. The PCE exposure in shops included in the study was evaluated independently (Ludwig *et al.*, 1983). The geometric mean of time-weighted-average exposures was 22 ppm PCE for machine operators and approximately 3 ppm for other workers.

In summary, a statistically significant excess of deaths from urinary tract cancer was observed in those workers that were potentially exposed to both PCE and petroleum solvents. Individuals employed in shops where PCE was the primary solvent did not have an increased risk of mortality from kidney or bladder cancer. Although these findings do not rule out PCE as the causative agent of urinary tract cancer, the data suggest that other factors or agents may have contributed to the development of neoplastic disease. CDHS stated in the Toxic Air Contaminant document "Health Effects of Tetrachloroethylene" that until studies are completed that include a thorough analysis and quantification of PCE exposures, epidemiological studies will not be useful for the assessment of the human health risks of PCE (CDHS, 1991).

Animal Studies

Two lifetime bioassays have been completed on PCE (NCI, 1977; NTP, 1986). Additionally, three other studies have addressed the question of PCE carcinogenicity (Rampy *et al.*, 1978; Theiss *et al.*, 1977).

The National Cancer Institute (NCI) conducted a study in which $B6C3F_1$ mice and Osborne Mendel rats were administered PCE in corn oil by gavage, 5 days/week for 78 weeks (NCI, 1977). The time-weighted average daily doses of PCE were 536 and 1072 mg/kg for male mice, 386 and 722 mg/kg for female mice, 471 and 941 mg/kg for male rats, and 474 and 949 mg/kg for female rats. PCE caused a statistically significant increase in the incidence of hepatocellular carcinomas in mice of both sexes and both dosage groups ($p < 0.001$). The time to tumor development was considerably shorter in treated than in control mice. In untreated and vehicle control mice, hepatocellular carcinoma were first detected at about 90 weeks. In comparison, hepatocellular carcinomas in male mice were detected after 27 weeks (low dose) and 40 weeks (high dose) and in female mice after 41 weeks (low dose) and 50 weeks (high dose) (Table 1). The median survival times of mice were inversely related to dose. For control, low dose and high dose male mice, their median survival times were 90 weeks, 78 weeks and 43 weeks, respectively; for female mice, their median survival times were 90 weeks, 62 and 50 weeks, respectively. Early mortality occurred in all groups of rats dosed with PCE. NCI (1977) determined that the early mortality observed in rats in this bioassay were inappropriately high and because the optimum dosage was not used, the rat results preclude any conclusions regarding the carcinogenicity of PCE in rats. In addition, the PCE used in the NCI mouse and rat bioassays had a purity of 99%, with epichlorohydrin (ECH) used as a stabilizer. It has been suggested that the presence of this contaminant may have directly contributed to tumor induction.

The most definitive study of the carcinogenic potential of PCE was conducted by Battelle Pacific Northwest Laboratories for the National Toxicology Program (NTP, 1986). In this experiment,

$B6C3F_1$ mice and F344/N rats were exposed to 99.9% pure PCE by inhalation, 6 hours/day, 5 days/week for 103 weeks. Mice were exposed to concentrations of 0, 100, or 200 ppm; rats were exposed to concentrations of 0, 200, or 400 ppm. Both exposure concentrations produced significant increases in mononuclear cell leukemia in female rats (incidence in control, 18/50 animals; in rats receiving 200 ppm, 30/50; and in rats receiving 400 ppm, 29/50). Treated male rats also developed mononuclear cell leukemia in greater numbers than controls (controls, 28/50 animals; 200 ppm, 37/50; 400 ppm, 37/50) [Table 1]. Male rats (at the 200 ppm and 400 ppm PCE exposure levels) exhibited an increased incidence of both renal tubular-cell adenomas and adenocarcinomas. Although the increases were not statistically significant, they appeared to be dose-related.

Brain glioma (a rare tumor of neuroglial cells) was observed in one male control rat and in four male rats that were exposed to 400 ppm PCE (NTP, 1986). This increase was not statistically significant. However, because the historical incidence of these tumors is quite low (0.2% at Battelle Laboratories), the increased incidence in treated animals in this study is noteworthy. Both concentrations of PCE produced a statistically significant increase of hepatocellular carcinomas in treated mice of both sexes ($p < 0.001$). The incidence of these carcinomas in male mice was as follows: controls, 7/49 animals; low-dose, 25/49; and high-dose, 26/50. The incidence of hepatocellular carcinomas in treated female mice was: controls; 1/48 animals; low-dose, 13/50; high-dose, 36/50. Hepatocellular adenomas occurred in both sexes of mice and at both concentrations of PCE (Table 1). The incidence of adenomas was not statistically significant. However, the combined incidence of hepatocellular adenomas and hepatocellular carcinomas was significant. In males, the combined incidence was: controls, 16/49 animals; low-dose 31/49; ($p = 0.002$); adenomas and carcinomas was: controls, 4/48 animals; low-dose, 17/50 ($p = 0.001$); and high-dose, 38/50 ($p < 0.001$).

Table 1: PCE-induced tumor incidence in mice and rats

Study	Species	Sex	Concentration or dose	Tumor response	
				Type[a]	Incidence
NCI, 1977	Mice	Males	0 mg/kg-d	HC	2/17
			536 mg/kg-d	HC	32/49*
			1072 mg/kg-d	HC	27/48*
		Females	0 mg/kg-d	HC	2/20
			386 mg/kg-d	HC	19/48*
			772 mg/kg-d	HC	19/48*
NTP, 1986	Mice	Males	0 ppm	HC; HAC	7/49 ; 16/49
			100 ppm	HC; HAC	25/49*; 8/49(NS)
			200 ppm	HC: HAC	26/50*; 18/50(NS)
		Females	0 ppm	HC; HAC	1/48 ; 3/48
			100 ppm	HC; HAC	13/50*; 6/50(NS)
			200 ppm	HC; HAC	36/50*; 2/50(NS)

[a] HC = hepatocellular carcinomas; HAC = hepatocellular adenoma; ML = mononuclear cell leukemia.
*$p < 0.001$, Fisher Exact Test; **Probability level, Life Table Analysis. NS = not statistically significant

The NTP (1986) determined that, under the conditions of the study, there was "clear evidence of carcinogenicity" of PCE for male F344/N rats, "some evidence of carcinogenicity" of PCE for female

F344/N rats, and "clear evidence of carcinogenicity" of PCE for both sexes of $B6C3F_1$ mice. IARC reevaluated the evidence of carcinogenicity of PCE in 1987 using data from the NTP study and concluded that there was sufficient evidence that PCE is carcinogenic to animals (IARC, 1987). Other studies on PCE included those by Rampy *et al.* (1978) and Theiss *et al.* (1977). Rampy *et al.* (1978) exposed male and female Sprague-Dawley rats to PCE by inhalation (300 or 600 ppm) 6 hours/day, 5 days/week for 12 months. Animals were subsequently observed for 18 months. Pathological changes in the liver or kidney were not observed. Theiss and coworkers studied the ability of PCE to induce lung adenomas in A/St male mice (Theiss *et al.*, 1977). Animals 6 to 8 weeks old were given 80, 200, or 400 mg/kg of PCE in tricaprylin (intraperitoneally) three times a week. Each group received 14, 24, or 48 injections. Treated animals did not exhibit a significant increase in the average number of lung tumors when compared to controls.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Perchloroethylene has been observed to induce mononuclear cell leukemia in male and female rats and liver tumors in male and female mice (NTP, 1986). CDHS (1992) decided that the tumor incidence data from this study were suitable for use in developing a quantitative risk assessment.

Methodology

Results from the 1986 NTP inhalation study were used as the basis for estimating the carcinogenic risk of PCE to humans. In this bioassay, PCE was 99.9% pure, and animals were exposed 6 hours/day, 5 days/week for 103 weeks. The mice in the 100 and 200 ppm dose groups were exposed to a time-weighted-average (TWA) of 16 and 32 ppm, respectively (e.g., 100 ppm × 6 hours/24 hours × 5 days/7 days). Similarly, rats in the 200 and 400 ppm dose groups were exposed to a TWA of 33 and 66 ppm, respectively.

The CDHS staff used the metabolized dose, adjusted to continuous lifetime exposure, to calculate the carcinogenic potency of PCE (CDHS, 1992). There are several uncertainties using this approach: 1) It was assumed that oxidative metabolism leads to the production of carcinogenic metabolites but the ultimate carcinogen(s) has not been well characterized. The metabolism of PCE is not well quantified in humans, and 20-40% of the absorbed PCE has not been accounted for. 2) The pharmacokinetic models used do not account for individual differences in metabolism and storage. The body burden depended on factors such as age, sex, exercise or workload, body mass, adipose tissue mass, pulmonary dysfunctional states, and individual differences in the intrinsic capacity to metabolize PCE.

Two pharmacokinetic models, the steady-state and the PB-PK approaches were used. They incorporated an 18.5% estimated applied dose as the fraction of the dose that is metabolized in humans. For the low-dose PCE risk assessment, the Crump multistage polynomial (Crump, 1984) was chosen.

This model, rather than a time dependent form of the multistage model, was chosen because most tumors were discovered only at the time of sacrifice, and survival in this study was relatively good. The cancer potency values derived using the two different pharmacokinetic approaches using the 1986 NTP rat and mouse studies ranged from 0.12 - 0.95 $(mg/kg\text{-}d)^{-1}$. When expressed as a function of human applied dose the values obtained ranged from 0.0025 to 0.093 $(mg/kg\text{-}d)^{-1}$. Using an estimated human weight of 70 kg, estimated breathing rate of 20 m^3/day and the PCE conversion factor of 1 ppb = 6.78 $\mu g/m^3$, the cancer unit risk values for PCE ranged from 0.2 - 7.2 $\times 10^{-5}$ $(ppb)^{-1}$. After considering the quality of the cancer bioassays and the uncertainty of human metabolism, CDHS (1992) decided that the best value for the PCE cancer unit risk was 4.0×10^{-5} $(ppb)^{-1}$ [5.9×10^{-6} $(\mu g/m^3)^{-1}$]. This value is derived from the tumor incidence data for the most sensitive species, sex, and tumor site, male mouse hepatocellular adenomas or carcinomas (NTP, 1986).

V. REFERENCES

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
SOLID WASTE AND EMERGENCY
RESPONSE

OCT 2 8 2009

MEMORANDUM

SUBJECT: The Toxicity of Perfluorooctanic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS)

FROM: Janine Dinan, Environmental Health Scientist
Office of Emergency Management (OEM)
Office of Solid Waste and Emergency Response (OSWER)

Dave Crawford, Environmental Scientist
Office of Superfund Remediation and Technology Innovation (OSRTI)
Office of Solid Waste and Emergency Response (OSWER)

TO: Glenn Adams, Chief
Technical Services Section
Superfund Division
US EPA Region 4

Background

PFOA and PFOS have been found at sites in EPA Region 4 and in other regions. As a result, Region 4 has asked the Headquarter's Office of Superfund Remediation and Technology Innovation (OSRTI) and the Office of Emergency Management (OEM) to recommend toxicity values.

On December 5, 2003, OSRTI released guidance (OSWER Directive 9285.7-53) establishing a three-tiered hierarchy of human health toxicity values. Tier 1 is EPA's Integrated Risk Information System (IRIS). Tier 2 is the provisional peer reviewed toxicity values (PPRTVs) completed for the EPA Superfund Program by the EPA Superfund Health Risk Technical Health Risk Support Center. Tier 3 are toxicity values from other credible sources such as other federal or State agencies. Three sources of Tier 3 toxicity values were identified in

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2003, but OSRTI also stated that additional Tier 3 sources may exist, and that additional Tier 3 sources may be identified in the future. As there are no toxicity values for PFOA or PFOS available in IRIS or as PPRTVs, this memorandum constitutes a Tier 3 consultation and recommends Tier 3 toxicity values for PFOA and PFOS.

Process

OSRTI and OEM consulted with several EPA program offices to discuss the use of the EPA Office of Water (OW) provisional health advisories as Tier 3 toxicity values. After weighing input from these offices, we make the following recommendations regarding the OW advisory and the interim oral non-cancer toxicity values for PFOA and PFOS.

Recommendations

On January 8, 2009 OW completed and released Provisional Health Advisories for PFOA and PFOS (See Attachment 1). Prior to the release of this assessment, OW invited, received and considered internal and external peer review comments on the then draft assessment. Although derived using methods that differ from the Superfund program's risk-based approaches, OSRTI and OEM find the OW provisional drinking water advisories of 0.4 µg/l for PFOA and 0.2 µg/l for PFOS credible as protective health-based concentrations for these contaminants in drinking water.

Because the OW provisional health advisories address only water consumption, oral reference dose values (RfDs), which can be used to address oral exposure to other media such as soil, were not developed. However, the methodology used by OW in deriving its provisional health advisories can also be used to derive subchronic RfD values for PFOA and PFOS, as shown below:

- **Perflurooctanoic Acid (PFOA)**

  For PFOA, the OW provisional health advisory relies on data from a sub-chronic study in mice (Lau, et al 2006) to derive a Benchmark Dose Level ($BMDL_{10}$) of 0.46 mg/kg-day[1]. When calculating toxicity values such as an RfD, a BMDL or a No Observed Adverse Effect Level (NOAEL) can be used to derive an RfD. In deriving an RfD for PFOA, certain numerical factors are applied to the BMDL to account for differences in the metabolism and sensitivity among test animals and humans to the effects of PFOA. Using the numerical factors presented in OW's provisional health advisory, a subchronic RfD can be developed, as follows:

[1] EPA toxicity assessments, including Integrated Risk Informaiton System (IRIS) assessments, using BML modeling in the derivation of an RfD typically use the 10% response level from the BML modeling ($BMDL_{10}$) to derive an RfD.

Subchronic RfD = $(BMDL_{10}) / UF_H * (UF_A = UF_{pharmacodynamic} * UF_{pharmacokinetic})$
= (0.46 mg/kg-day) / 10 * (3 * 81)
= **2E-4 mg/kg-day**

UF_H = a factor of 10 to account for variations in the dose-response (i.e., sensitivity) among humans to the effects of PFOS

UF_A= a factor to account for differences in the metabolism of PFOA in mice vs. humans
- $UF_{pharmacodynamic}$ = a factor of 3 to account for variations in the dose-response among mice to the effects of PFOA
- $UF_{pharmacokinetic}$ = a factor of 81[2] to account for differences in the rate of clearance of PFOA in mice vs. humans

- **Perfluorooctane Sulfonate (PFOS)**

For PFOS, the OW provisional health advisory relies on data from a sub-chronic study in monkeys (Seacat, et al. 2002) to derive a NOAEL of 0.03 mg/kg-day. As with PFOA, certain numerical factors are applied to the NOAEL to account for differences in the metabolism and sensitivity among test animals and humans to the effects of PFOS. Using the numerical factors presented in OW's provisional health advisory, a subchronic RfD can be developed, as follows:

Subchronic RfD = $(NOAEL) / UF_H * (UF_A = UF_{pharmacodynamic} * UF_{pharmacokinetic})$

= 0.03 mg/kg-day / 10 * (3 * 13)
= **8E-5 mg/kg-day**

UF_H = a factor of 10 to account for variations in the dose-response (i.e., sensitivity) among humans to the effects of PFOS
UF_A= a factor to account for differences in the metabolism of PFOS in monkeys vs. humans
- $UF_{pharmacodynamic}$ = a factor of 3 to account for variations in the dose-response among monkeys to the effects of PFOS
- $UF_{pharmacokinetic}$ = a factor of 13[3] to account for differences in the rate of clearance of PFOS in monkeys vs. humans

Currently, OEM has not established removal action levels for PFOA or PFOS as the basis for considering alternate water supplies, nor have these contaminants been addressed in the Regional Screening Levels for Chemical Contaminants at Superfund Sites. However, the Tier 3 sub-chronic RfDs presented in this memorandum may be used in the Superfund program's risk-based equations to derive Removal Action Levels and/or Screening Levels for water and other media, as appropriate.

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[2] See Attachment 1, page 4 for additional details about this UF.
[3] See Attachment 1, pages 4 and 5 for additional details about this UF.

Please be aware that the recommendations made in this memorandum may be modified by OSRTI and OEM as the state of the science evolves with respect to deriving toxicity values and determining protective concentrations of PFOA and PFOS. Such changes may include the availability of an IRIS or a PPRTV assessment and/or the promulgation of a Safe Drinking Water Act Maximum Contaminant Level by OW.

Questions related to the use of this memorandum and its recommendations may be directed to Dave Crawford (703-603-8891) and to Janine Dinan (202-564-8737) in OEM.

Attachment 1